The American Journal of Medicine

February 1952

The American Journal of Medicine

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, N. Y. Yearly Subscription, $12.00 U. S. A.; $14.00 Canada and Latin American countries; $15.00 Foreign. Single Numbers $2.00; Symposia Numbers $4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. February, 1952—Volume XII, No. 2. Copyright, 1952, by The American Journal of Medicine, Inc.

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

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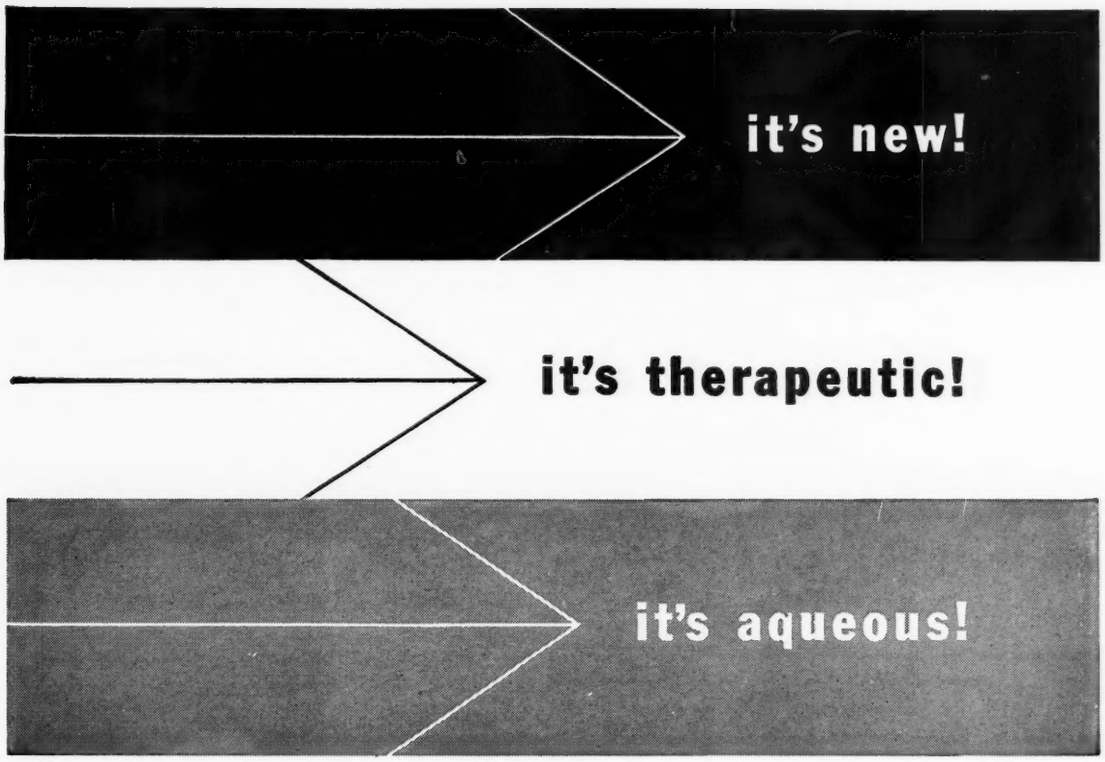

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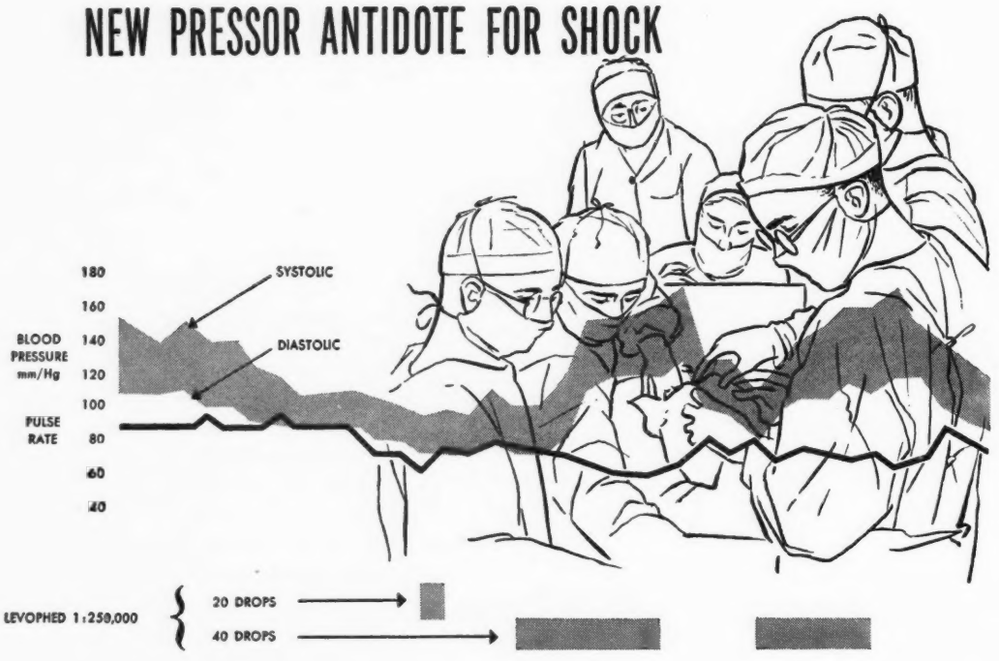

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WRITE FOR DETAILED INFORMATION.

1. *Phillips, O.C., and Nicholson, M. J.:* Surg. Clin. North Am., *30:705, June, 1950.*
2. *Wilson, C.M., and Bassett, R.C.:* Univ. Michigan Med. Bull., *16:57, March, 1950.*

Levophed, trademark reg. U. S. & Canada

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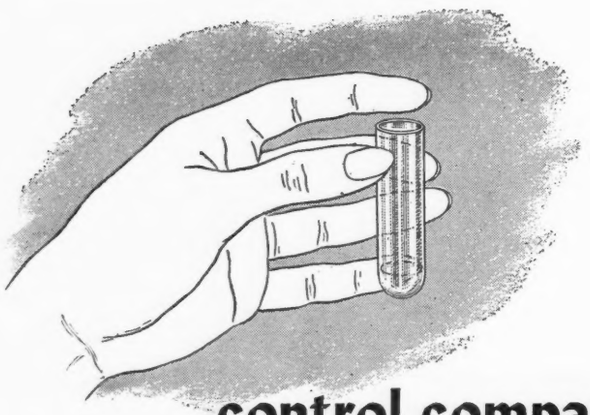

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Sprague, R. G.: Cortisone and ACTH, Am. J. Med. *10*:567, 1951.

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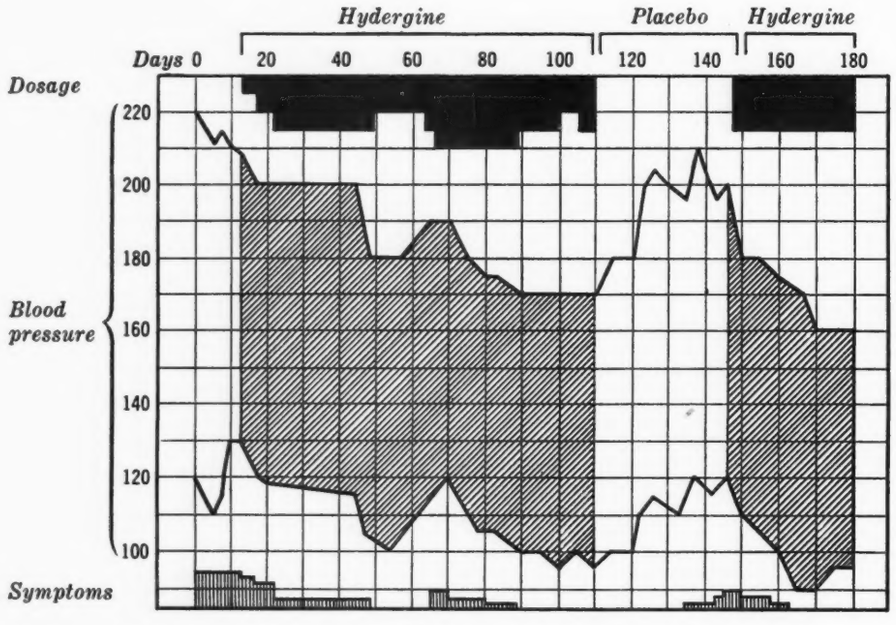
Hydergine—A New Product and New Approach To Peripheral Vascular Diseases

Investigation of a new approach to the treatment of peripheral vascular diseases and hypertension has established the practical value of hydrogenated ergot alkaloids.

Development of these alkaloids in the SANDOZ LABORATORIES, study of their properties and evaluation of their usefulness by clinicians are the groundwork for the therapeutic application of Hydergine ampuls. Hydergine consists of hydrogenated derivatives of the three alkaloids in the "ergotoxine group": dihydroergocornine, dihydroergocristine and dihydroergokryptine.



Replacement of Hydergine by placebos caused blood pressure to rise immediately while resumption of treatment with Hydergine produced renewed fall in blood pressure.

The above typical case is taken from our research files. Additional data shows a peripheral vasodilator action, adrenergic blockade, and central dampening of pressoreceptive reflexes by Hydergine.

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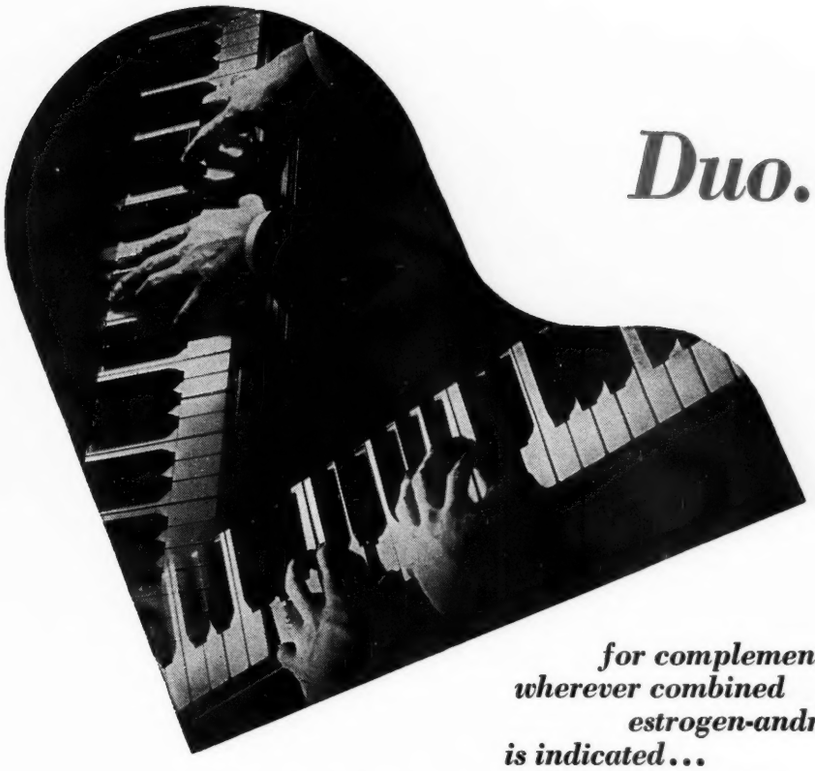

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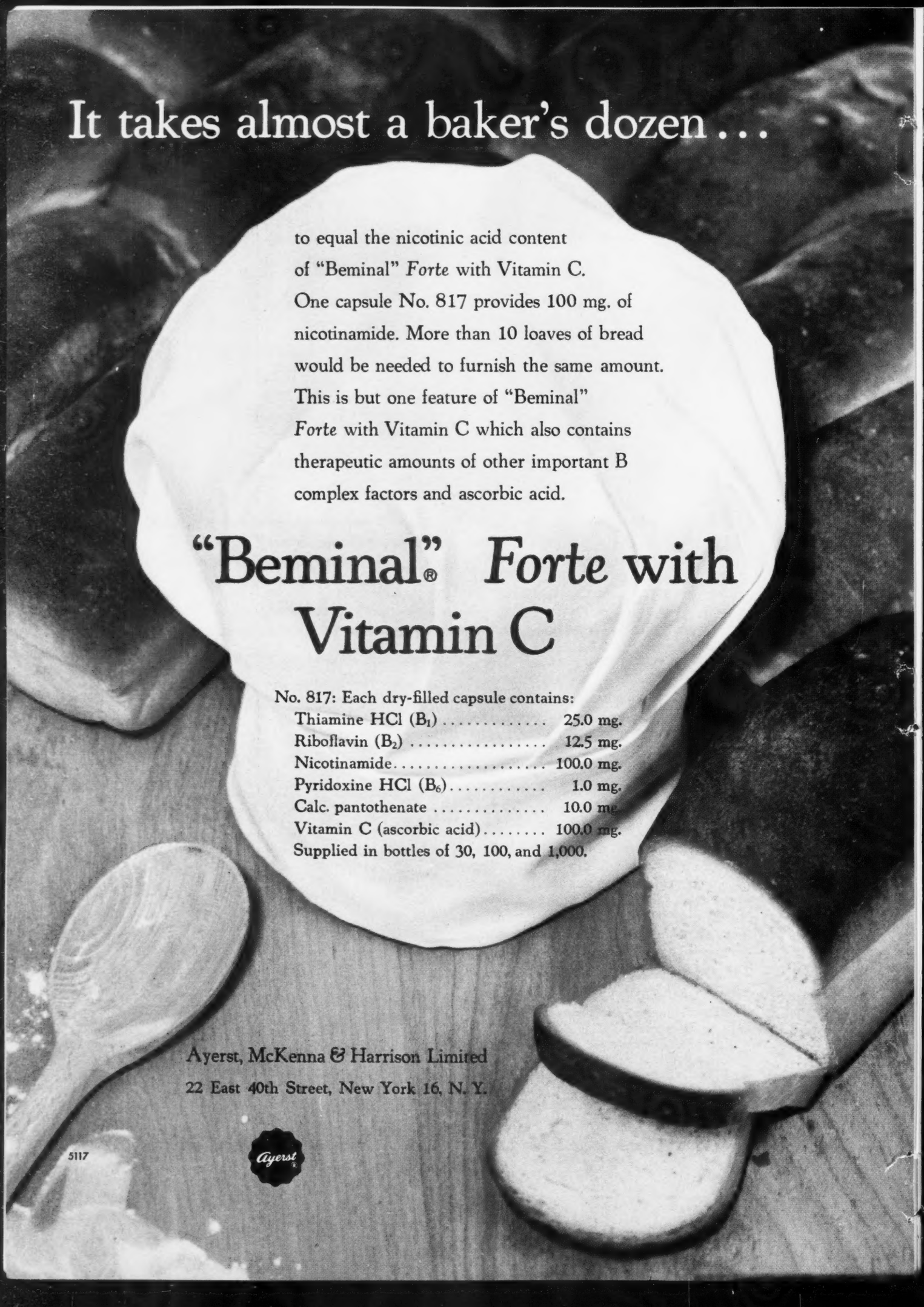
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---

1. Longacre, A. B.: P-92 Penicillin; Report of a Very Low Reaction Rate in Therapy with a New Penicillin Salt, Antibiotics & Chemotherapy *1*:223 (July) 1951.

2. Kadison, E. R.; Ishihara, S. J., and Waters, T.: A New Form of Penicillin with Anti-Allergic Properties, Am. Pract. & Digest Treat. *2*:411 (May) 1951.

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(pure khellin)

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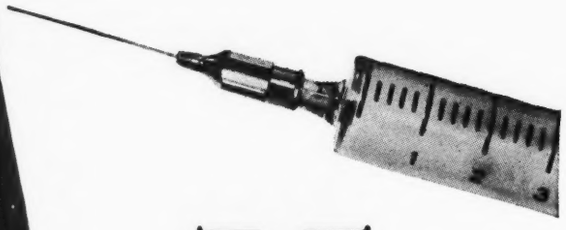
a potent coronary vasodilator



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Tryptar introduces a new therapeutic principle of selective physiologic debridement. Without attacking normal tissue, Tryptar digests only necrotic tissue and pyogenic membranes, induces satisfactory granulation and promotes healing within a short time . . . even in varicose ulcers of many years' duration.

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1. Reiser, H. G., et al.: Arch. Surg. 63: 568-575 (Oct.) 1951.

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MALTBIE... first
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Chart shows increase in biliary secretion after injection of sodium dehydrocholate, as compared to various bile salts.
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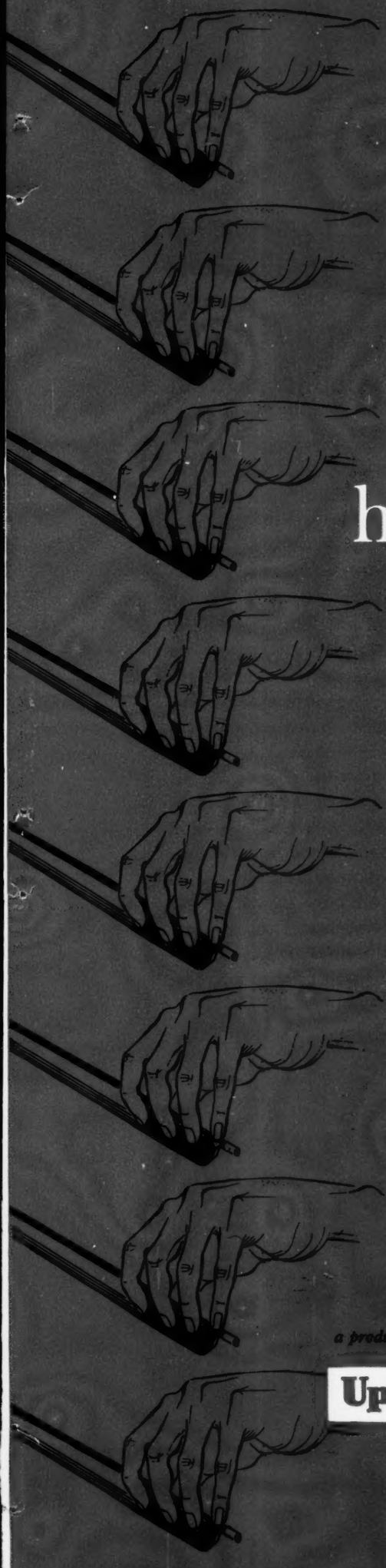

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multiple action hema*tonic*

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Vitamin B_{12} Activity	5.0 micrograms
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Thiamine Hydrochloride	2.0 milligrams
Riboflavin	2.0 milligrams
Pyridoxine Hydrochloride	0.5 milligram
Nicotinamide	10.0 milligrams
Ascorbic Acid	35.0 milligrams

dosage: Adults — 3 tablets daily.
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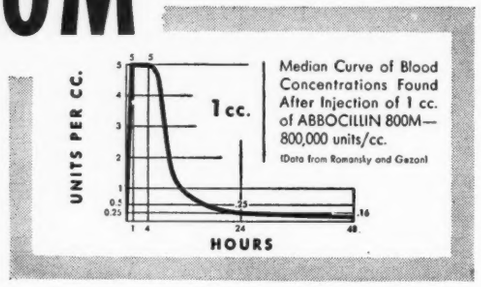

from among
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AUREOMYCIN

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It readily passes into the cerebrospinal fluid, the presence of meningitis making little difference in its concentration.

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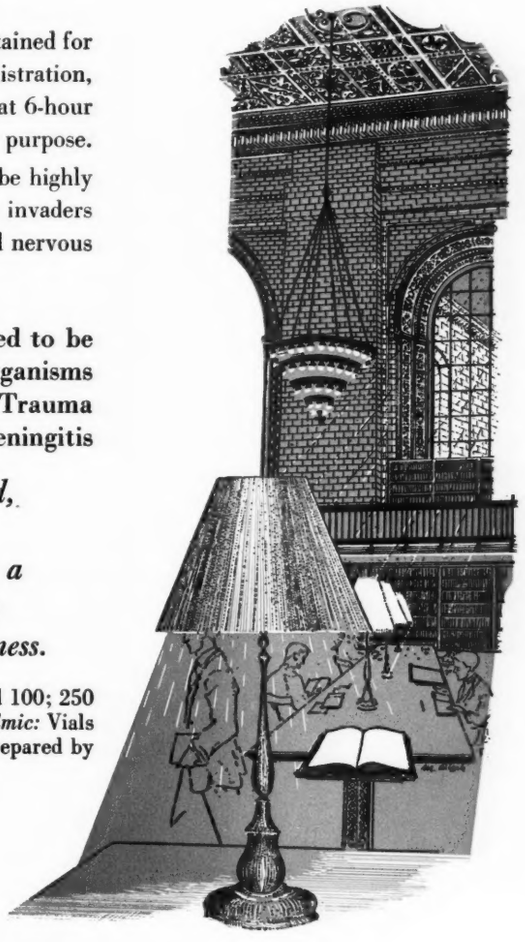

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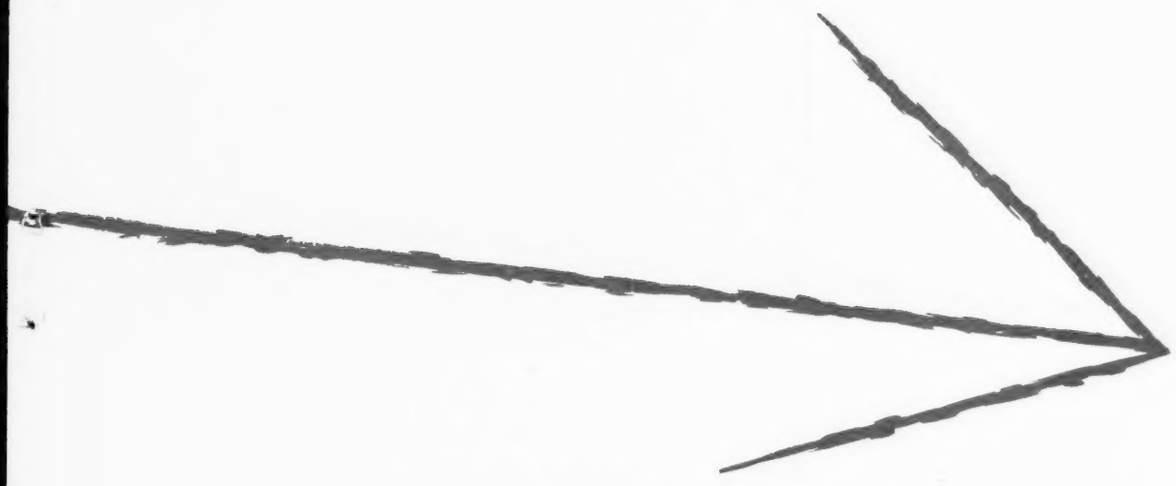

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(500,000 units of penicillin per teaspoonful)*

Highest potency liquid oral penicillin available — Most economical liquid oral penicillin available

Fully effective on convenient 8 to 12 hour dosage schedule

New DRAMCILLIN-250 with Triple Sulfonamides . . . *and*

New DRAMCILLIN-250 TABLETS with Triple Sulfonamides

(250,000 units of penicillin and 0.5 Gm. mixed sulfonamides† per teaspoonful or tablet)*

Effective two-fold attack against wider range of microorganisms

Minimizes possibility of development of drug-resistant organisms

DRAMCILLIN-250—(250,000 units* per teaspoonful).

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†0.167 Gm. each of sulfadiazine, sulfamerazine and *sulfacetimide* (the sulfa of choice as the third component)

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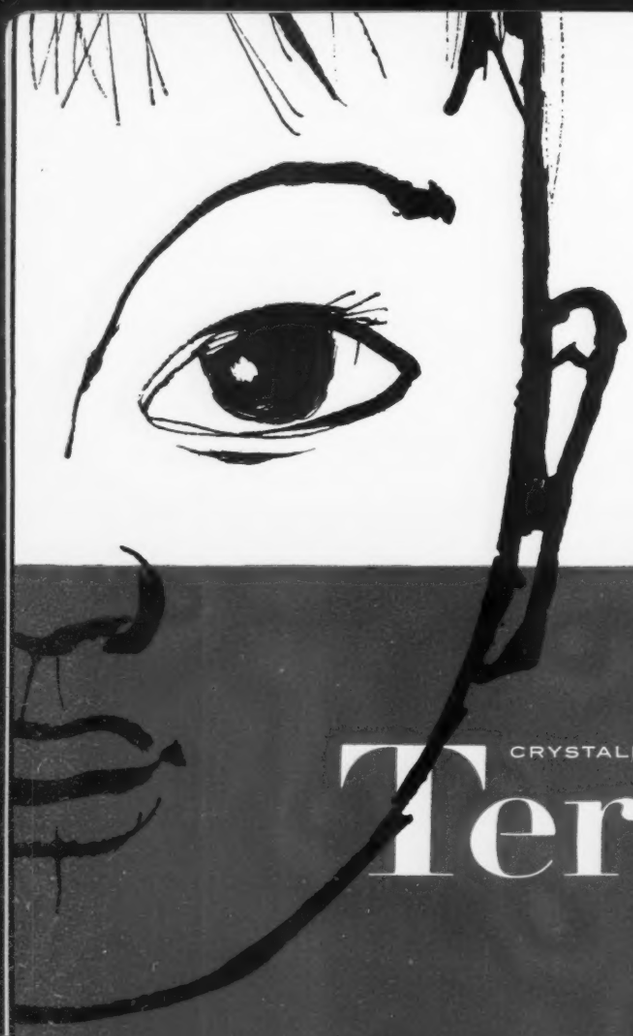

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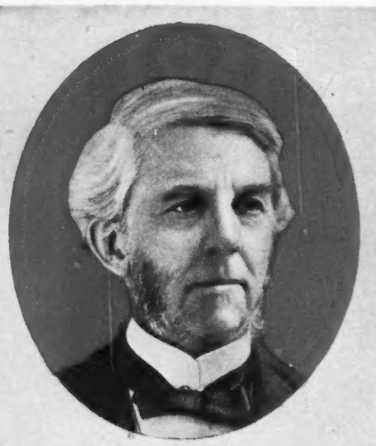

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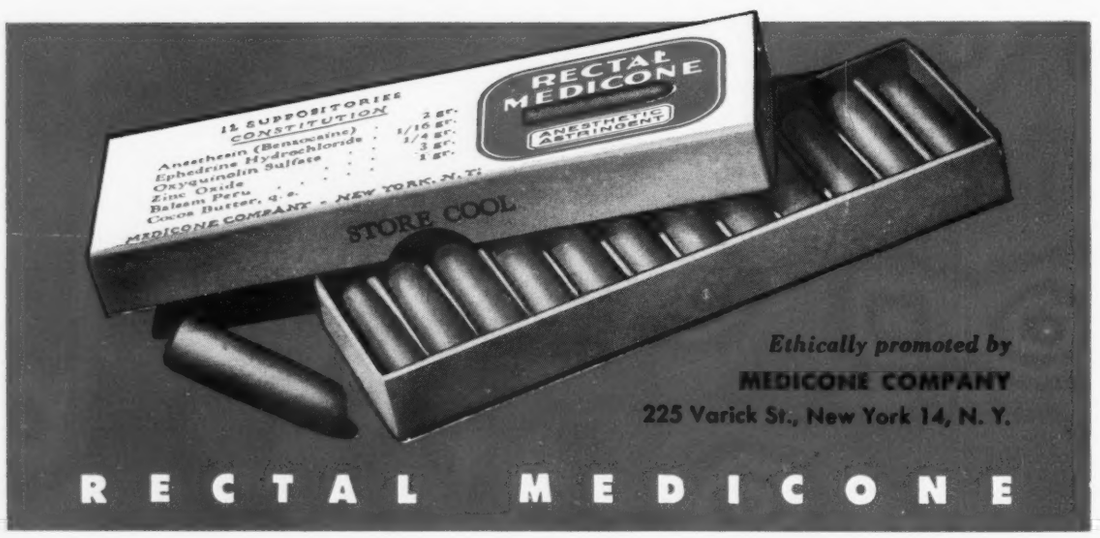
22	ACUTE	22 RELIEF IN ALL CASES
16	CHRONIC	10 SATISFACTORY RESPONSE *(4 of the 16 cases required surgery)*



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anticholinergic gives
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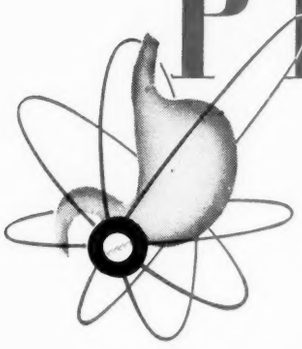

for peptic ulcer

greater specificity
hitherto unobtainable freedom from side effects
wider flexibility of dosage
reduces gastric motility and secretion
relieves pain

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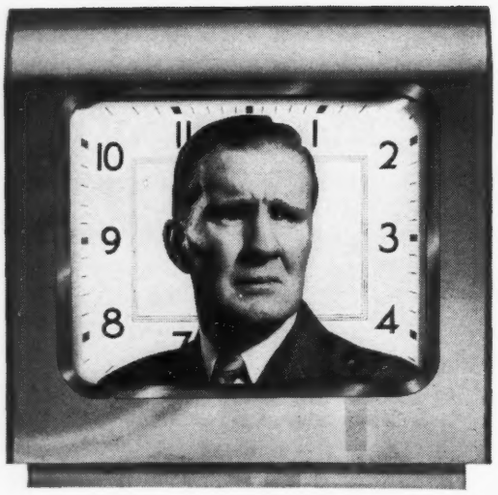

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Urinary Tract Symptoms

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Pyridium may be administered concomitantly with crystalline dihydrostreptomycin sulfate, penicillin, the sulfonamides, or other specific therapy to provide the twofold benefit of symptomatic relief and anti-infective action.

Pain and burning decreased in 93% of cases . . .*

Urinary frequency relieved in 85% of cases . . .*

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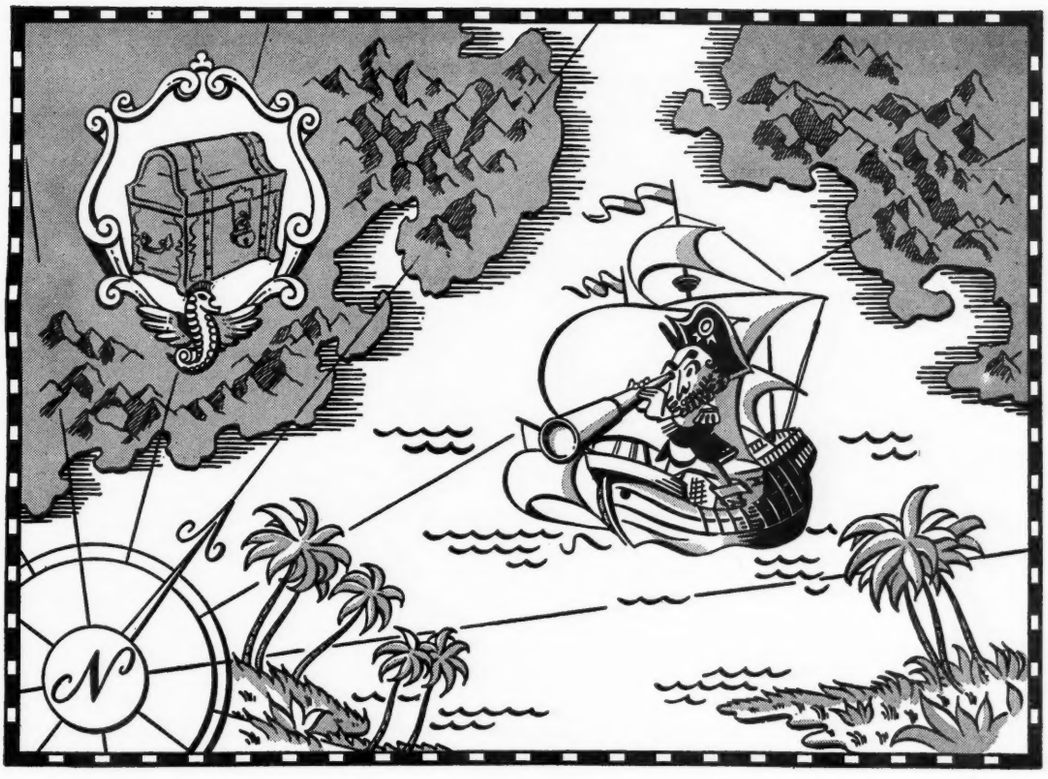

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"Accurate testing of hearing is an essential bedrock on which to build."—Kerridge, Phyllis M. Tookey, *Can Physics Help the Deaf Child?*—The Lancet 1:104-108 (January 12), 1935.

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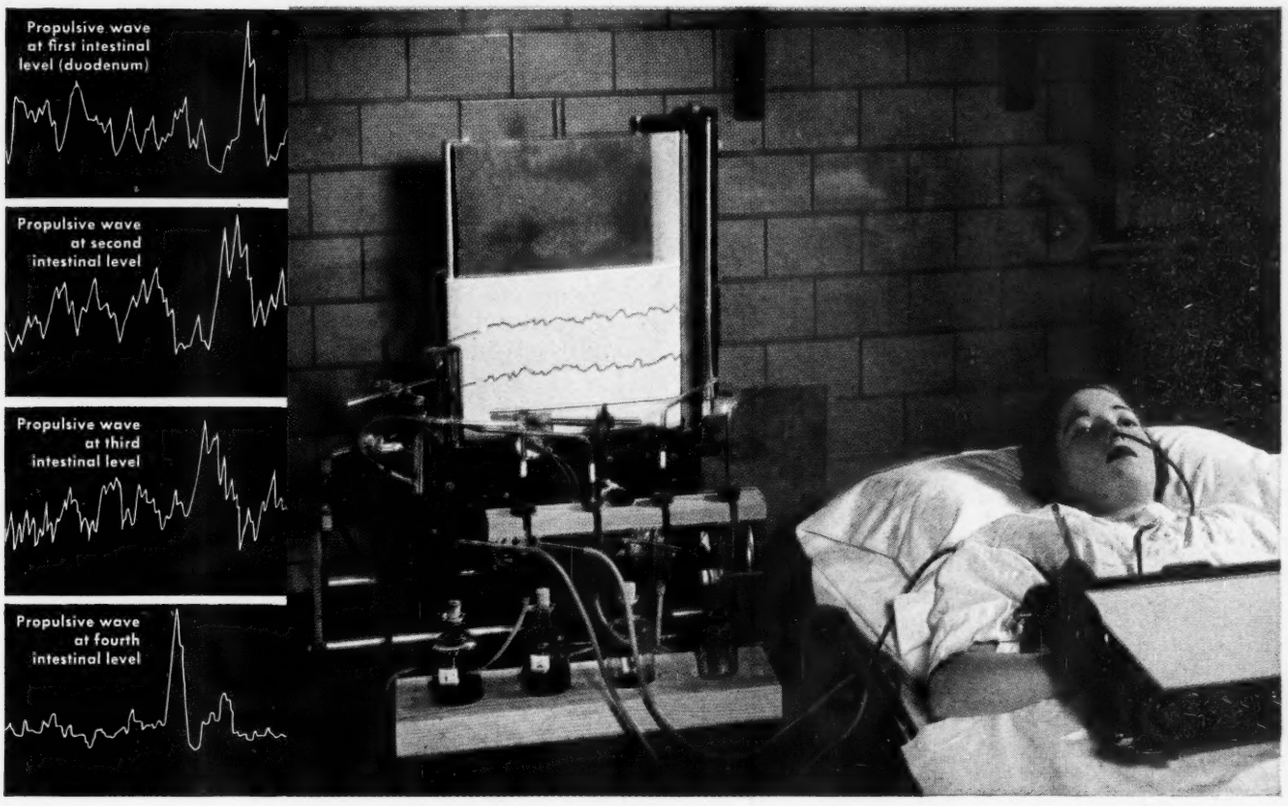

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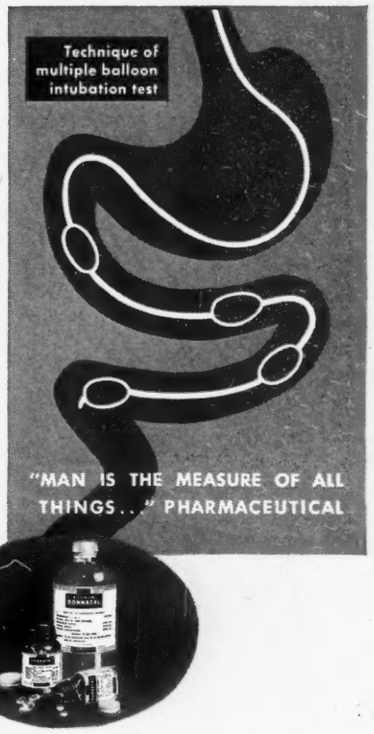

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REFERENCES: 1. Kammandel, H. et al.: Bull. N. Y. Med. Coll., Flower & Fifth Ave. Hosps. (in press). 2. McGavack, T. H. and Klotz, S. D.: Bull. N. Y. Med. Coll., Flower & Fifth Ave. Hosps., 9:61, 1946. 3. Weissberg, J. et al.: Am. J. Dig. Dis., 15:332, 1948.

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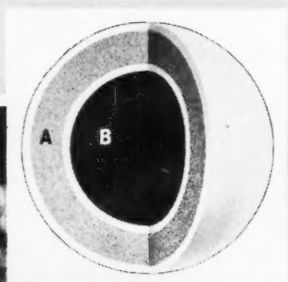

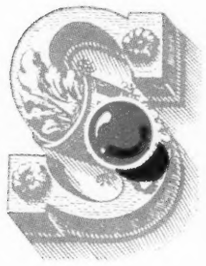

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References: 1. Hufford, A.R.: J.A.M.A. 123:259 (1943)
2. Talisman, M.R.: Amer. Jrl. Obst. & Gyn. 46:146 (1943)

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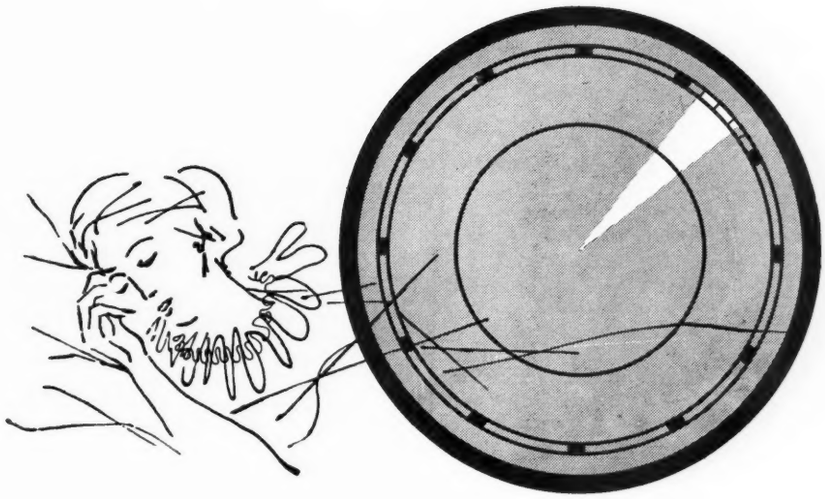

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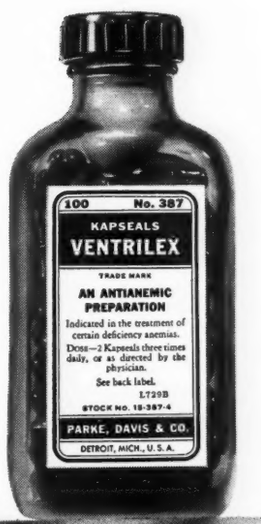

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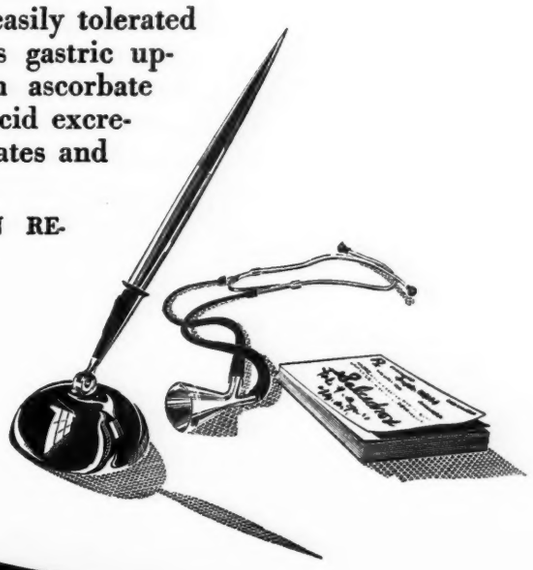

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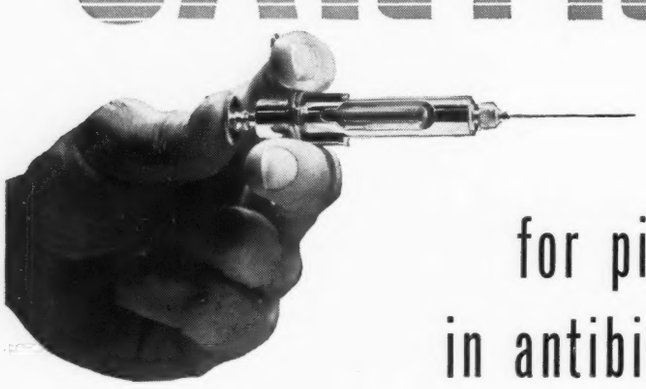

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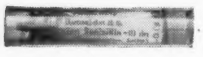

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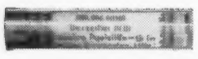

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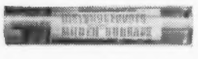

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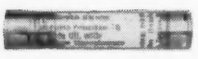

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The American Journal of Medicine

VOL. XII FEBRUARY, 1952 No. 2

Editorial

Ancillary Factors in Virus Infection

THE recent interesting report by Jordan and Mirick[1] calls attention to ancillary factors which may promote active viral infections or modify their course. Using material, presumably icterogenic, from patients with infectious hepatitis, Jordan and Mirick were able to produce in mice a disease transmissible in series and showing marked liver lesions. Intraperitoneal injections of hepatotoxic material such as monocrotaline or urethane were given as well and seemed to promote the ease with which infection took place.

Surveying this field in general, it turns out that the following agents may be of importance in promoting or modifying viral infection, namely, exposure to cold, physical stress, bacteria, chemical agents and hormones.

The chapter on bacteria in relation to virus infection begins, of course, with the story of hog cholera; Welch's papers can still be read with the greatest interest.[2] Although there was no doubt in Welch's mind that the hog cholera bacillus and the bacillus of swine plague were etiologic agents, it is of interest that the swine plague organisms, even when fed in large amounts to normal pigs, did not produce disease. Now it is known, of course, that the essential cause of hog cholera is a virus which lowers the bars to invasion by the hog cholera and swine plague bacilli. This sort of specific association is well illustrated by an interesting disease of rats, so-called ulcerative cecitis. This disorder, which clinically seems closely analogous to regional ileitis in man, may at times occur in a high percentage of aging animals in any rat colony. There is enlargement of mesenteric nodes and a progressive ulceration with inflammatory infiltration confined to the cecum which eventually becomes a scarred mass of diseased tissue with only a small lumen. Cysts containing a clear, watery fluid often are found surrounding the lesions. The cecal contents are liquid and have a curious foul odor. In all the reported outbreaks a strain of salmonella has been consistently found in pure culture.[3] There is reason, however, to think that this organism is only an ancillary agent to some other unknown and perhaps viral cause. If the strain of salmonella isolated from the feces is fed to healthy rats in small amounts, the animals remain well and eventually develop cecitis no more frequently than uninoculated controls. If the salmonella, on the other hand, is fed in larger amounts, an acute diffuse necrotizing enteritis is produced; if the animal survives, it again seems not especially susceptible to cecitis. Furthermore, the clear fluid in the cysts surrounding the lesion contains no salmonella and indeed is sterile on ordinary culture.[4] Streptomycin, as well as sulfonamides, seemed to prevent or delay the development of ulcerative cecitis.

The elucidation of the relation of Hemophilus influenzae suis to swine influenza by Shope[5] is an intensely interesting story. Here the virus alone produces only a feeble version of the full-blown natural disease in which the hemophilus plays an essential part. Although no role can be assigned to the influenza bacillus in human influenza, it has been clearly shown that

[1] JORDAN, J. and MIRICK, G. S. Hepatitis of mice, of presumed viral origin. *Bull. Johns Hopkins Hosp.*, 89: 326, 1951.

[2] WELCH, W. H. Remarks on Hog Cholera and Swine Plague. Papers and Addresses by William Henry Welch, vol. II, p. 86. Baltimore, 1920. Johns Hopkins Press.

[3] BLOOMFIELD, A. L. and LEW, W. Significance of salmonella in ulcerative cecitis of rats. *Proc. Soc. Exper. Biol. & Med.*, 51: 179, 1942.

[4] BLOOMFIELD, A. L. et al. Relation of a specific strain of salmonella to ulcerative cecitis of rats. *Proc. Soc. Exper. Biol. & Med.*, 71: 457, 1949.

[5] SHOPE, R. E. The influenzas of swine and man. *Medicine*, 15: 453, 1936.

H. influenzae may become widely prevalent in the throats of the population at large during and after epidemics of pandemic influenza.[6]

Other interesting examples of the association of bacteria with viral diseases are the cases of Streptococcus MG and primary atypical pneumonia and of infectious hepatitis complicated by secondary invasion with salmonella. Some years ago Mirick and his associates observed a high incidence of a non-hemolytic streptococcus with certain special characteristics in the throats and sputum of patients with virus pneumonitis.[7] This association was frequent enough to suggest some etiologic relationship although recent studies do not seem to substantiate these findings at present. It is quite possible that Str. MG played a role in virus pneumonia for a time but has been washed away on the shifting tides of bacterial parasitism. Havens and Werner[8] pointed out, in certain situations, the close association of Salmonella choleraesuis with infectious hepatitis, in some cases with bacteremia.

Thus it appears that ordinary bacteria may potentiate the production of disease by a virus as in the case of swine influenza, or the virus infection may seem to let down the bars to bacterial invasion, as with salmonella following hepatitis. In other cases the exact position is not clear.

How other influences may affect viral infections is well illustrated by the common cold which in certain people is definitely precipitated by chill or exposure. The latest thought on this subject supposes certain individuals to be carriers of cold virus. Chilling in the case of some of these people seems to act as what Andrewes[9] calls "the jolt." It seems to be the factor which lets down the bars. So, too, in carriers of herpes virus all sorts of disorders from lobar pneumonia to Hodgkin's disease may precipitate a crop of fever blisters.

With poliomyelitis it seems now to be clear that heavy physical exertion during the early stages of infection may promote more extensive paralysis than would otherwise occur.[10] With this strange disease we are also tempted to believe that following a "saprophytic spread" (Topley) of virus through a community some unknown influence may precipitate an outbreak of many cases widely scattered. In animal pathology this sort of thing is extensively documented. An example is that of pneumonia virus of mice which may be carried harmlessly until passed through a series of animals.[11] We cannot undertake to go into the complexities of virus interference which no doubt will turn out to play an important role in human pathology.

It would take us too far afield to discuss in detail the influence of the newer adrenal hormones on viral infections but no doubt much important information will soon be accumulated. Southam and Babcock[12] review the subject to date and report that large doses of cortisone greatly increased the susceptibility of mice to lethal infection with West Nile and other viruses. However, the general point to be made by this discussion is that virus infections cannot be thought of as simple problems; they may be modified or conditioned by a great variety of extraneous influences.

ARTHUR L. BLOOMFIELD, M.D.

[6] BLOOMFIELD, A. L. The significance of the influenza bacilli. *Bull. Johns Hopkins Hosp.*, 33: 172, 1922.

[7] MIRICK, G. S. et al. Biological characteristics of Streptococcus MG. *J. Exper. Med.*, 80: 391, 1944.

[8] HAVENS, W. P., JR. and WERNER, H. A. Infectious hepatitis complicated by secondary invasion with salmonella. *J. Clin. Investigation*, 25: 45, 1946.

[9] ANDREWES, C. H. Adventures among viruses. *New England M. J.*, 242: 179, 1950.

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Clinical Studies

Effects of Cortisone in Sarcoidosis*

A Study of Thirteen Patients

LOUIS E. SILTZBACH, M.D.
New York, New York

THE etiology of sarcoidosis still eludes us, as does the definitive treatment. Part of the difficulty with respect to therapy stems from the unpredictability of spontaneous remissions. This accounts for the many transitory successes reported at one time or another with such agents as calcium salts, gold, arsenicals, potassium iodide, chaulmoogra oil, antileprol and tuberculin. During the last five years patients attending the Sarcoidosis Clinic of the Mount Sinai Hospital have been treated with penicillin, streptomycin, promin, diasone, aureomycin, radiation therapy, nitrogen mustard and calciferol without apparent effect.

A previous communication[1] described a case of sarcoidosis in which severe bilateral uveal tract involvement had led to virtual blindness. A fifteen-week course of intramuscularly administered cortisone led to dramatic and sustained recovery of vision and shrinkage of enlarged mediastinal lymph nodes as well.

This paper concerns the effects of cortisone in thirteen patients. Of interest were histologic changes noted in tissues which were removed while the drug was being given or soon afterward. Fourteen post-treatment biopsy specimens from eight patients were available for study. During the course of this study several workers[2–7] have reported on the influence of cortisone and ACTH in sarcoidosis.

METHODS

Before therapy was started patients were observed for at least four weeks. During that time studies of particular interest in sarcoidosis were made and these were repeated in the course of therapy and afterward. Among these studies were clinical and roentgen examinations, Nickerson-Kveim skin tests with biopsies of the test areas, tuberculin tests and estimations of serum protein levels. Repeated ophthalmologic examination, spinal puncture and bronchoscopy were carried out when indicated.

Biopsies of involved tissues were performed when possible shortly before treatment was begun. When enlarged peripheral lymph nodes were excised, sites with a chain of nodes were chosen, when available, in order that nodes could be left behind to be observed under therapy. This also permitted repetition of biopsy from the original area after a suitable interval under therapy. For biopsies of Nickerson-Kveim skin test areas a small-bore punch was used so that portions of the test area could be left relatively undisturbed for future excision. Lung biopsies were performed through an intercostal incision under general anesthesia.

The course of cortisone therapy ranged from four to fifteen weeks. Three patients received the drug for twenty-eight to forty days, seven patients for forty-one to seventy days, and three patients for seventy-one to 106 days. The daily dose was 100 to 150 mg., the larger amount being given when supply permitted. Five patients received the drug intramuscularly and eight orally.

Sodium intake was restricted to 200 mg. a day for hospitalized patients and 500 mg. for ambulatory patients. A potassium supplement was given in the form of the chloride, 3 gm. daily. The indicated clinical and laboratory studies for side effects of cortisone were made periodically. At the time of this report ten patients had been observed for one to eleven months following cessation of therapy. Three patients were nearing the end of their course.

Patient Material. There were nine female and four male patients. Eight were white and

* From the Medical Services of the Mount Sinai Hospital and the Pulmonary Division of Montefiore Hospital, New York, N. Y. Support for this study was received from the General Research Fund of the Mount Sinai Hospital and from the Henry L. Moses Fund of Montefiore Hospital.

five Negro. Ten were under forty years old. All but one of the patients gave evidence of active sarcoidosis. Seven patients were severely disabled as a result of the illness. Four had loss of vision in one or both eyes. One of these four had a spinal cord lesion as well. Three patients had incapacitating pulmonary symptoms and one of these three had static lesions. Six patients with milder complaints had recent spread of disease.

Duration of the illness, as measured by the first clinical evidence, ranged from three months to five years. Some of the patients had been under close observation for months and years.

Table 1 shows the sites of organ involvement determined clinically and by biopsy. Twelve patients had multiple organ systems involved. Eight had peripheral lymphadenopathy and seven had mediastinal lymph node enlargement. There were pulmonary lesions in seven, ocular lesions in six, cutaneous lesions in two and subcutaneous in two. Three had hepatomegaly and two had splenomegaly. The parotid glands, the central nervous system and the bronchial tree were each involved in one instance. For two patients tissue biopsy confirmation was lacking but the clinical picture and positive Nickerson-

TABLE 1

CLINICAL STATUS OF THIRTEEN PATIENTS WITH SARCOIDOSIS PRIOR TO CORTISONE THERAPY

Case No.	Duration of Illness	Site of Involvement	Serum Albumin/ Serum Globulin (gm. %)	Nickerson-Kveim Intradermal Reaction	Tuberculin Reaction	Length of Course and Total Dosage of Cortisone	
						Days	Gm.
I	8 mo.	Uveal tract, both eyes; mediastinal lymph nodes	4.8/2.6	Positive	Negative in 1:100 dil.	106	13.7
II	8 mo.	Subcutaneous tissues of both arms*	4.8/2.3	Negative	Negative in 1:100 dil.	39	4.7
III	3 yr.	Peripheral lymph nodes,* mediastinal lymph nodes	4.6/2.2	Positive	Negative in 1:100 dil.	40	4.5
IV	1 yr.	Peripheral lymph nodes,* lung (r), mediastinal lymph nodes (r), parotid glands, uveal tract – both eyes (q), hepatomegaly	3.8/5.9	Positive	Negative in 1:100 dil.	77	10.2
V	18 mo.	Peripheral lymph nodes,* lungs, mediastinal lymph nodes, uveal tract – left eye, hepatosplenomegaly	3.9/4.1	Positive	Negative in 1:100 dil	63	8.5
VI	4 yr.	Lungs (q), mediastinal lymph nodes (q)	4.8/2.1	Positive	Negative in 1:10,000 dil., positive in 1:100 dil.	28	3.7
VII	20 mo.	Peripheral lymph nodes,* uveal tract – left eye, central nervous system, lungs (q), hepatomegaly	3.3/3.9	Positive	Negative in 1:100 dil.	67	7.0
VIII	4 yr.	Peripheral lymph nodes,* skin*	3.4/2.2	Positive	Negative in 1:100 dil.	65	9.2
IX	8 mo.	Lungs,* mediastinal lymph nodes	3.8/4.2	Positive	Negative in 1:100 dil.	73	7.7
X	18 mo.	Lungs, peripheral lymph nodes*	4.4/3.4	Positive	Negative in 1:100 dil.	49	6.3
XI	1 yr.	Bronchial wall,* peripheral lymph nodes,* mediastinal lymph nodes (q), lungs, uveal tract – right eye (q), splenomegaly	4.2/3.8	Positive	Negative in 1:100 dil.	63 (receiving ACTH)	8.0
XII	2 yr.	Uveal tract – both eyes, skin*	4.2/2.3	Positive	Negative in 1:10,000 dil.; positive in 1:100 dil.	57 (course being completed)	7.0
XIII	4 mo.	Subcutaneous tissue of abdominal wall,* peripheral lymph nodes*	3.3/2.3	Positive	Negative in 1:100 dil.	55 (course being continued)	8.5

*Tissue from which pretreatment biopsy was obtained.
(q) = quiescent lesion; (r) = regressing lesion.

Kveim reactions supported the diagnosis. Six patients had an elevation of serum globulin exceeding 3.0 gm. per cent. The Nickerson-Kveim skin test showed a positive reaction in twelve of the thirteen patients. The tuberculin test was negative in a 1:10,000 dilution in all instances and positive in a 1:100 dilution in only two.

primarily progressive lesions, was chosen for study. Reversal of trend had to be prompt in order to be considered more than coincidental.

All thirteen patients improved subjectively or objectively under therapy but in none did the result approach a cure. The response to cortisone was irregular and often transitory. In the same patient some sites regressed while others remained refractory.

TABLE II

CLINICAL RESPONSE TO CORTISONE THERAPY ACCORDING TO SITES OF INVOLVEMENT

Site of Involvement*	No. of Patients	No. with Signs of Clinical Regression under Cortisone Therapy	No. with Relapse at Listed Site after Cortisone Therapy†
Peripheral lymph nodes	8	8	2
Mediastinal lymph nodes	4	2	0
Lungs	4	3	2§
Uveal tract	4	3	1
Liver	3	0	-
Spleen	2	0	-
Subcutaneous tissues	2	2	1
Skin	1‡	1	0
Parotid	1	1	0
Central nervous system	1	0	-
Bronchial wall	1	1 (?)	0

*Pulmonary and mediastinal lymph node lesions were regressing in one patient before cortisone therapy was started. Quiescent lesions present at the beginning of therapy included pulmonary, 2; mediastinal lymph nodes, 2; and ocular lesions, 2. None of these are listed in this table.

†One patient with quiescent pulmonary and mediastinal lymph node lesions which remained unchanged during cortisone therapy had symptomatic relapse after the drug was halted.

‡One patient not shown in this category had a cutaneous nodule removed in its entirety before cortisone therapy was started.

§One patient whose chest x-ray showed little change during therapy but who improved clinically had symptomatic relapse when the drug was halted.

RESULTS

Sarcoidosis has an episodic clinical course. Its exacerbations and remissions are unpredictable and often the disease progresses at one site while receding at another. Upswings and downswings usually extend over periods of months and years rather than days and weeks. Therefore, in assessing the value of cortisone therapy the drug's effect on active lesions, and

Of seven patients with severe disability five obtained significant relief of their major symptoms during therapy. The other two also showed regressive phenomena but these were limited to lesions of lesser import. In no patient could progression of lesions be detected during treatment, a period of four to fifteen weeks—which is a short span, however, in so chronic a disease. In general, fresh lesions seemed to be more

amenable to therapy than older ones although lesions known to have existed as long as two years also proved responsive.

Post-treatment Observations. Ten patients have been observed from one to eleven months after therapy. Seven have relapsed; three have not. Of the seven, three suffered return of signs and symptoms just as severe as those present before therapy but the other four had only mild setbacks and are still in a better state than they were beforehand.

As to the three who did not relapse, two had regression at all sites under therapy and have maintained their gains for four weeks and four and a half months, respectively. The remaining patient who did not relapse had only received benefit to minor sites of involvement and, although these benefits endured, the major disability was uninfluenced.

When relapses occurred, they did so as early as two weeks and as late as three months after treatment.

Table II lists the clinical response during and after therapy of active lesions in various organs. Regressive and quiescent lesions which may have coexisted are omitted.

Peripheral Lymph Nodes. Eight patients had enlarged peripheral nodes involving one or more chains. They were known to have been present for one month to one year. Under therapy all showed some degree of shrinkage. Usually the first sign of recession occurred during the second week, and by the end of one month the nodes were barely palpable. When there was massive enlargement shrinking went on at times for as long as eight weeks.

Nodes in different chains regressed at the same tempo. An exception was a single node in an inguinal group: It was still fairly large after six weeks of therapy whereas its mates had receded after four weeks (Case XIII).

Although some nodes became palpable again after the drug was stopped, they did not reenlarge significantly except in one patient (Case VIII). In this instance cervical nodes which had been massive before treatment and had entirely receded under therapy reappeared in some areas three weeks after a sixty-five-day course of therapy was completed. They were only about one-fourth their pretreatment size, however, and did not grow larger during the following month. In another patient (Case III) the originally enlarged submaxillary nodes remained impalpable for eight months after therapy but a cervical node became palpable at a previously uninvolved site three months after therapy was concluded. In brief, peripheral lymph node lesions were uniformly benefited and relapse was infrequent after cessation of therapy.

Mediastinal Lymph Nodes. Of seven patients with this localization four were considered to have active and progressive lymphadenopathy. The other three had nodes which either were receding beforehand or had already receded and remained static for a long period. Table II shows that of the four patients with active disease in this location only two obtained shrinkage under therapy. The nodes did not entirely disappear in either case but became substantially smaller.

Nodes began to shrink about the tenth day and reached minimal size after one month. The nodes have not enlarged again in eleven months' and one month's observation, respectively. In the two patients in whom the mediastinal nodes were not affected peripheral nodes of recent appearance shrank promptly.

The patient with receding nodes continued to show recession under therapy and the static nodes of two other patients remained unchanged. These are not shown in the table. In sum, mediastinal nodes were apparently benefited when they were of relatively recent onset but older nodal enlargements were not.

Lungs. There were seven patients with pulmonary involvement but only four disclosed progression of lesions on serial chest films before therapy was begun. Partial or complete regression occurred in three and no significant changes were noted on the films of the fourth. The clearing began as early as the tenth day and was most pronounced after four to eight weeks. The single patient whose chest film showed no change nevertheless experienced dramatic relief from cough and severe dyspnea which had been increasing for eighteen months. Symptomatic relapse occurred two weeks after the drug was stopped and by the seventh week the patient's symptoms were almost as severe as before treatment.

Of three patients with roentgenographic clearing one is still under therapy, another maintained his improved state for four weeks afterward and one had recurrence of fine linear and nodular densities which had completely cleared under therapy. The relapse occurred six weeks after treatment.

Three patients with pulmonary lesions are omitted in Table II under this heading because their lesions were either regressive or static. One of these, with resorbing lesions, showed continuous regression under therapy and has had no recurrence during four and a half months following therapy. The improvement cannot be ascribed to cortisone, however, since the regression was well under way before therapy was started. The two patients with static pulmonary lesions on serial chest films showed no change during therapy or afterward. One had marked relief of dyspnea for two months following therapy but then symptomatic relapse occurred.

In summary, fresh pulmonary lesions appeared to be responsive but older ones were not. Symptomatic and roentgenographic relapse occurred in a fair proportion after the drug was stopped.

Eyes. Of six patients with ocular involvement two had lesions which had already become quiescent when therapy was started and do not appear in Table II. The four with active disease of the eye had uveal tract lesions causing almost complete loss of vision in one or both eyes. The symptoms dated back eight months to two years and, under standard treatment, the lesions had continued to extend. The lesions were bilateral in two cases and unilateral in the other two.

Systemic cortisone therapy effected various degrees of improvement in three of the four patients. The patient who did not benefit had phthisis bulbi and later an enucleation was performed. Two of the three patients who did benefit had significant recovery of visual acuity with concomitant regression of lesions. The third, with advanced scarring, also showed considerable clearing of granulomatous deposits but an opaque membrane occluded the pupil and prevented any improvement in vision. When visual acuity increased under therapy, the improvement occurred promptly. Hyperemia and neovascularization also decreased rapidly but only later did corneal opacities, iritic nodules and clouding of the vitreous respond. In one instance clearing of the vitreous required nine weeks of therapy.

One patient who had made a dramatic recovery later had a mild relapse. Three weeks after intramuscular therapy was discontinued the uveitis became slightly active again. This was effectively controlled by cortisone drops administered for nine weeks. No other flareup occurred in the following eight months without drug. The second patient had no recurrence during four and a half months after therapy but she has no effective vision in the affected eye because of extensive scarring. The third patient maintains moderate improvement in vision while still under therapy.

In essence, ocular lesions responded dramatically when the uveitis had not progressed to irreversible scarring.

Other Sites of Involvement. Liver and spleen: Three patients had hepatomegaly and two had splenomegaly. There was no change in size of these organs while the patient received therapy or thereafter.

Subcutaneous tissues: One patient had large masses beneath the skin of both arms for eight months (Darier-Roussy sarcoidosis). After ten days' treatment the masses began to recede and by the fifth week they had almost completely disappeared. However, relapse occurred one month after treatment and the masses were again as large as they were before. Another patient had numerous four month old clusters of nodules under the skin of the abdomen. These nodules regressed slowly and were still present after fifty-five days' treatment. Therapy is being continued.

Skin: Two patients had localized cutaneous lesions. One had the entire lesion removed by biopsy before starting therapy. There was no recurrence of the lesion. The other patient had had a nasal lesion for four years. This had begun to spread four weeks before therapy began. In nine days the lesion began to pale and flatten, and regression was sustained for the rest of a sixty-five-day course of therapy. The lesion did not entirely clear, but seven weeks after therapy it remained pale and flat.

Parotid glands: One patient had huge parotid glands of one month's duration. With therapy the glands began to recede after one week and after three weeks were much smaller. The patient was unable to appear for his supply of drug on the twenty-fifth day of therapy and there was a lapse in treatment for one week. On his return the parotid glands were again huge but once the drug was resumed the glands once more subsided in two weeks. After eight weeks the glands were no longer palpable, and there has been no relapse during four and one-half months' post-treatment observation.

Spinal cord: Involvement at this site, an uncommon one in sarcoidosis, occurred in a patient who had a segmental lesion of the

thoracic spinal cord with paraparesis of both lower extremities and ataxia of eleven months' duration. Transitory improvement occurred from the seventh to the seventeenth day of therapy and then the patient's symptoms returned in full force. She has been observed for three and a half months following therapy and is still chair-ridden.

Bronchial wall: Involvement at this site in one patient caused narrowing of a bronchus with pulmonary infection and bronchiectasis distal to it. Cortisone was administered along with antibiotic agents. After three weeks the bronchus was patent again and remained so for the following ten weeks of therapy.

Effect of Treatment on Serum Proteins. Of six patients with serum globulin levels above 3.0 gm. per cent four showed a fall in concentration during therapy; two did not. In two patients with a fall the concentration dropped to 3.0 gm. per cent or less. Four of the six patients had an inverted albumin-globulin ratio. In three, however, the albumin again exceeded the globulin at the end of therapy.

Effect on the Nickerson-Kveim Reaction. Three patients still showed the cutaneous papules of a positive Nickerson-Kveim reaction when cortisone therapy was undertaken. In all three the papules faded and flattened within three to seven days, leaving slightly indurated pigmented areas.

TABLE III

COMPARISON OF BIOPSIES BEFORE AND AFTER CORTISONE THERAPY

Case No.	Pretreatment Biopsy			Post-treatment Biopsy		
	Site	Interval Prior to Cortisone Therapy	Microscopic Appearance	Site	Days of Cortisone Therapy	Microscopic Appearance
I	Nickerson-Kveim test area	3 wk.	Sarcoid-like granuloma (Fig. 1A.)	Nickerson-Kveim test area	5	Sarcoid-like granuloma; no change
				Nickerson-Kveim test area	29	Non-specific scar tissue replacement; no granuloma (Fig. 1B.)
II	Subcutaneous tissue of arm	3 mo.	Epithelioid cell granulomas; no fibrosis (Fig. 2A.)	Subcutaneous tissue of arm	34	Scar tissue with few nests of epithelioid cells; granuloma absent (Fig. 2B.)
IV	Cervical lymph node	6 mo.	Epithelioid cell granulomas; few small foci of hyalinization (Fig. 3A.)	Inguinal lymph node	70	Marked hyalinization; sparse epithelioid cell granulomas (Fig. 3B.)
				Submental lymph nodes (2)	77	Marked hyalinization; sparse epithelioid cell granulomas
V	Femoral lymph node	2 wk.	Epithelioid cell granulomas; same appearance as node removed 1 yr. earlier; no hyalinization (Fig. 4A.)	Femoral lymph node	39	Complete hyalinization; no epithelioid cell granulomas seen (Fig. 4B.)
VII	Cervical lymph node	7 mo.	Epithelioid cell granulomas; minute foci of hyalinization	Cervical lymph node	75*	Moderate increase of hyalinization; epithelioid cell granulomas persist
				Enucleated eye	78†	Some fibrosis and hyalinization of still numerous granulomas
IX	Pulmonary tissue	1 wk.	Epithelioid cell granulomas; some fibrosis and hyalinization (Fig. 6A.)	Pulmonary tissue	59	Marked fibrosis and hyalinization of lung; granulomas still present but less numerous (Fig. 6B.)
XI	Axillary lymph node	3 wk.	Epithelioid cell granulomas; small areas of hyalinization	Axillary lymph node	26	Slight increase of hyalinization; epithelioid cell granulomas numerous
				Inguinal lymph node	58	Slight increase of hyalinization; epithelioid cell granulomas numerous
	Bronchial wall	3 wk.	Non-caseating epithelioid cell granulomas under bronchial mucosa	Bronchial wall	60	Single non-caseating tubercle beneath mucosa
XIII	Subcutaneous nodule from abdominal wall	7 wk.	Epithelioid cell granulomas; marked fibrosis and hyalinization in some areas; areas of necrosis present; no caseation	Subcutaneous nodule from abdominal wall	43	Epithelioid cell granulomas persist; no discernible increase in extent of hyalinization or fibrosis
	Inguinal lymph node	7 wk.	Epithelioid cell granulomas; marked fibrosis and hyalinization in some areas	Inguinal lymph node	43	Epithelioid cell granulomas persist; no discernible increase in extent of hyalinization or fibrosis

*Biopsy taken 8 days after completion of a 67-day course.

†Enucleation performed 11 days after completion of a 67-day course.

Post-treatment Biopsies. Biopsies of involved tissues were performed in eight patients during therapy or shortly afterward. Fourteen specimens were available for study and could be compared with pretreatment sections, except for an enucleated eye. (Table III.) Biopsies had been obtained one week to three months prior to treatment in all but two cases, IV and VII, in which the interval was six and seven months, respectively.

The post-treatment biopsy specimens were from the following sources: peripheral lymph nodes, seven; pulmonary tissue, one; bronchial wall, one; subcutaneous tissue, two; Nickerson-Kveim reaction papules, two; and the enucleated eye. The specimens were obtained at intervals of five to seventy-eight days after cortisone therapy was started.

Ten of the specimens showed changes in the microscopic picture when compared with pretreatment sections. All the changes were similar to those seen in spontaneous healing of sarcoidosis lesions.

Five specimens from four patients showed pronounced changes. One lymph node which had shriveled grossly showed apparently complete replacement of the epithelioid cell granulomas by hyalinized connective tissue. Only scattered giant cells remained. Two pretreatment biopsies, one from the same chain, had shown no hyalinization. (Fig. 4A and B.)

Two lymph nodes from another patient, which nodes likewise had diminished, showed the same extensive fibrosis and hyalinization but here there were a few small residual tubercles. (Fig. 3A and B.) A specimen of subcutaneous tissue revealed marked fibrosis. (Fig. 2A and B.) The only remnants of large granulomas which had been present previously were scattered small nests of epithelioid cells. The subcutaneous masses had receded grossly, and they recurred one month after therapy.

A Nickerson-Kveim papule which had regressed under therapy showed replacement of sarcoid-like tubercles by scar tissue. (Fig. 1A and B.)

In two other specimens the fibrosis and hyalinization were not quite so prominent and a fairly large number of tuberculoid granulomas still remained. One specimen was a lymph node which had shrunk and the other was a wedge of pulmonary tissue which was removed by open thoracotomy. (Fig. 6A and B.) In the latter instance the surgeon had noted markedly fewer nodules in the lung on palpation, and striking resorptive changes had been evident on serial chest x-ray films made during therapy. The fibrotic and hyaline changes in two lymph nodes which were removed successively from one patient were slight even though shrinkage had been noted clinically.

Four biopsy sections were little altered from their respective pretreatment sections. These were the following: a subcutaneous nodule which had decreased to about half its pretreatment size and a lymph node which had not shrunk much each showed little change; a residual tubercle appeared in a bronchoscopic specimen from a bronchus which had narrowed from sarcoidosis involvement and widened under therapy; and a Nickerson-Kveim papule which was beginning to flatten and pale showed no recession of the granulomas five days after therapy. The enucleated eye showed many granulomas, some of them undergoing fibrosis and hyalinization similar in degree to that shown by the patient's shrunken lymph node when removed one week earlier.

Five patients had shown some degree of hyalinization in one or more of their pretreatment biopsy specimens. (Table III.) The hyalinization was slight and limited to small foci except in an abdominal subcutaneous nodule and an inguinal lymph node in Case XIII in which it was quite extensive. There was no recognizable increase of fibrosis and hyalinization in the post-treatment sections of that patient's specimens.

In essence, the post-treatment biopsies showed hyalinization in all specimens but two: the five-day Nickerson-Kveim papule and the bronchoscopic specimen. In only one patient with hyalinization already prominent in the pretreatment sections was no ascertainable increase found.

Side Effects of Cortisone Therapy. In one instance the drug had to be discontinued after twenty-eight days because the patient, normally high-strung, experienced severe insomnia and heightened mental tension marked by extreme talkativeness. The symptoms disappeared promptly when the drug was stopped. In a second patient a full-blown psychosis of a schizoid type developed five days after termination of a sixty-three-day course of treatment. She was transferred to a psychiatric hospital and the symptoms cleared spontaneously after two weeks. She was discharged from that institution after a stay of three and one-half weeks

and had no return of mental symptoms during the following three months. As far as could be determined there had been no previous symptoms of mental difficulty.

Hyperglycemia associated with a diabetic type of glucose tolerance curve was noted in one patient on the seventy-seventh day of his course. The level of blood glucose subsequently receded as the dosage of the drug was tapered off.

Rounding of the face developed in all patients and two had mild acne. None of the patients exhibited significant sodium or water retention and determinations of blood electrolytes in hospitalized patients revealed no important deviations from normal levels.

CASE REPORTS

CASE 1.* *Bilateral uveitis with virtual blindness; mediastinal lymphadenopathy.* P. D., A thirty year old Negro housewife, was admitted to Montefiore Hospital on April 5, 1950, with severe bilateral ocular sarcoidosis and enlargement of mediastinal lymph nodes. The ocular lesions were eight months old and in spite of standard treatment vision had deteriorated to a point where the patient had to be led into the hospital. On admission her visual acuity was limited to seeing hand movements. The cornea of the right eye was almost completely opaque in the inferior temporal zone and in the pupillary area. In the left eye dense opacities covered the lower half of the cornea. The vitreous was cloudy in both eyes. Slit-lamp examination revealed deep corneal infiltrates with bilateral vascularization. The posterior surfaces of the cornea were studded with unpigmented keratic precipitates.

Chest roentgenogram revealed enlargement of lymph nodes in both hilar and in the right paratracheal areas. This finding had been noted six months before admission (October, 1949) but was not present on a routine survey film made nine months earlier than that. The peripheral lymph nodes were not enlarged. On the skin of the right forearm were two six month old Nickerson-Kveim reaction papules, one 9 mm. and the other 6 mm. in diameter. A portion of each test area was excised and revealed the typical sarcoid-like structure of a positive reaction. (Fig. 1A.)

Cortisone was given intramuscularly for fifteen weeks starting May 5, 1950. The patient received a daily dose of 150 mg. during most of the course or 13.7 gm. in all. There was a dramatic effect upon visual acuity. After one day's treatment the patient could count fingers at 2 feet and by the twelfth day she could walk about the ward unaided. On the sixteenth day she could read large type in a newspaper and by the end of the fourth week the vision in each eye was 20/100 or 49 per cent of normal binocular vision.

This recovery was paralleled by objective improvement. In the second week the injection of the scleral and ciliary vessels disappeared and in the third week the vascularization of the cornea receded and the keratic precipitates diminished. In the fourth week the corneal opacities dwindled. In the ninth the vitreous cleared and the patient maintained her improved status throughout the rest of the course.

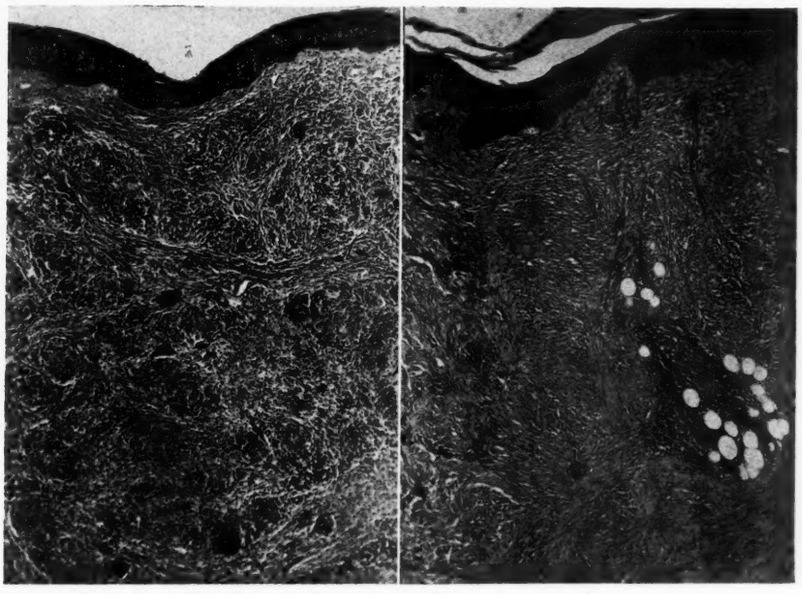
The enlarged hilar and right paratracheal lymph nodes began to shrink on about the tenth day. After one month the nodes in the right hilar and paratracheal regions were no longer visible and the nodes at the left hilar region, although still enlarged, were less than half their pretreatment size. This shrinkage was maintained.

On the third day the red-brown papules of the six month old Nickerson-Kveim skin test began to flatten and pale. Punch biopsy removing a small core of the test area performed on the fifth day showed little histologic change, but on the twenty-ninth day biopsy of a skin test area not previously disturbed showed that the tuberculoid granulomas had regressed and were replaced by fibrous scar. (Fig. 1B.)

The patient left the hospital with 76 per cent of normal binocular vision. She had a mild exacerbation of her uveitis three weeks after cortisone was stopped but this was easily controlled with cortisone drops which were continued nine weeks.

The patient has been observed for eleven months following systemic therapy and there has been no relapse. She still has some residual scarring of the cornea and a quiescent uveitis. The lymph nodes in the left hilar area remain slightly prominent but those on the right never again became visible. The patient is employed

* This case is presented in greater detail elsewhere.[1] The author is grateful to Drs. Eileen K. Hite and Raymond E. Weston of the Medical Divison, Montefiore Hospital, for their aid in the clinical and metabolic studies.



1A 1B

FIG. 1. Case I. A, photomicrograph (× 110) of a section of skin taken from a Nickerson-Kveim intradermal test area before cortisone therapy; the cutis is permeated by epithelioid cell granulomas with giant cells. No caseation is present. Appearance is similar to naturally occurring sarcoidosis of the skin except for presence of more inflammatory cells here. B, photomicrograph (× 110) of a section of skin taken from a Nickerson-Kveim intradermal test area after twenty-nine days of cortisone therapy; the granulomatous nodules are no longer visible, being replaced by non-specific scar tissue. A collection of lymphocytes is seen at the lower right.

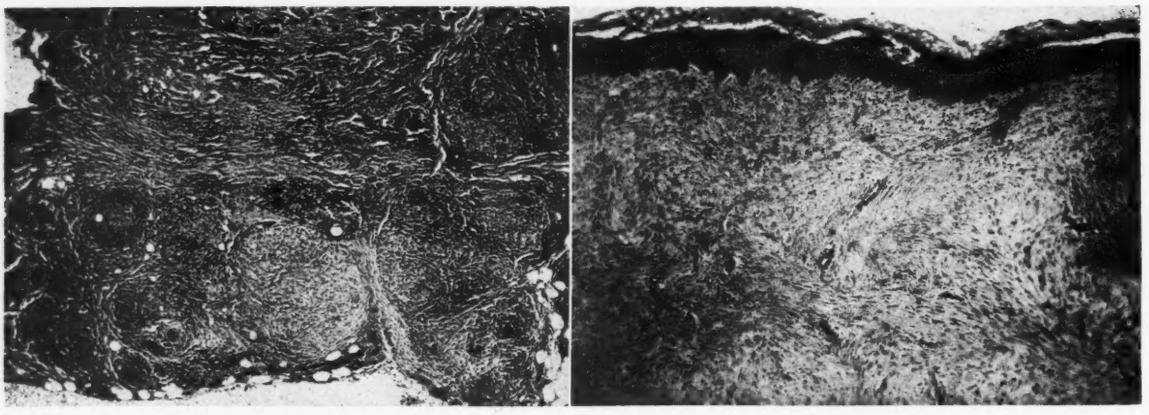
at her regular household duties with little limitation.

Comment. Cortisone effectively suppressed the inflammatory components of the ocular disease such as serous and plastic exudates and vascularization, and this action brought about dramatic recovery of vision. The extent and severity of the ocular lesions had made it seem likely that loss of vision would be permanent. The shrinkage of the mediastinal lymph nodes suggested that the tuberculoid granulomas were also affected by the drug. This was supported by microscopic evidences of regression in the Nickerson-Kveim skin test areas.

CASE II. *Slowly enlarging subcutaneous masses in both arms (Darier-Roussy sarcoidosis).* D. G., a twenty-four year old white female, was admitted to the Mount Sinai Hospital on September 20, 1950, complaining of slowly enlarging masses in both upper arms. The masses were first noted nine months earlier when the skin over the deltoid regions became red and tender and remained so for some weeks. After that the patient felt areas of firmness deeper in the skin and these grew slowly larger. Her general condition was excellent. She had not lost weight or had any fever. Physical examination disclosed firm, flat, non-tender, slightly granular confluent masses in the deltoid regions of both arms. Each mass measured about 8 by 10 cm. The skin over the masses was not altered. There was no lymphadenopathy. Biopsy of the subcutaneous masses in both arms revealed large, non-caseating, epithelioid cell tuberculoid granulomas studding the subcutaneous tissue. (Fig. 2A.) There was no evidence of fibrosis or hyalinization.

Cortisone was administered for thirty-nine days starting September 20, 1950. The dose was 150 mg. a day for the first ten days and 100 mg. thereafter or 4.75 gm. in all. In ten days the masses began to shrink in both arms. By the fifth week the masses could not be felt. The one remaining abnormality was that the skin felt a little less supple than in neighboring areas. Biopsy of the subcutaneous tissue was repeated on the thirty-fourth day. This revealed non-specific scar formation without tuberculoid granulomas. (Fig. 2B.) The only residua of the granulomas previously seen were a few nests of epithelioid cells.

One month after termination of therapy the



2A 2B

FIG. 2. Case II. A, photomicrograph (× 120) of a section of subcutaneous and cutaneous tissue excised before cortisone therapy; large, plump epithelioid cell tubercles without caseation permeate the tissue. B, photomicrograph (× 120) of a section of subcutaneous and cutaneous tissue removed thirty-four days after cortisone therapy; there is a non-specific young scar response without tuberculoid granulomas. A few scattered epithelioid cell nests were present but are not visible here.

masses enlarged to their former size and they have slowly progressed during the ensuing eight months.

Comment. Striking regression of tuberculoid granulomas in the subcutaneous tissue did not prevent their full-blown recurrence one month afterward.

CASE III. *Enlarged mediastinal lymph nodes; recent flareup of peripheral nodes.* L. S., a thirty-six year old white housewife, was admitted to the Sarcoidosis Clinic of the Mount Sinai Hospital in January, 1948, with enlarged mediastinal lymph nodes which had been found a month earlier in a survey chest film. The patient had had an attack of erythema nodosum in 1946 but otherwise had been well.

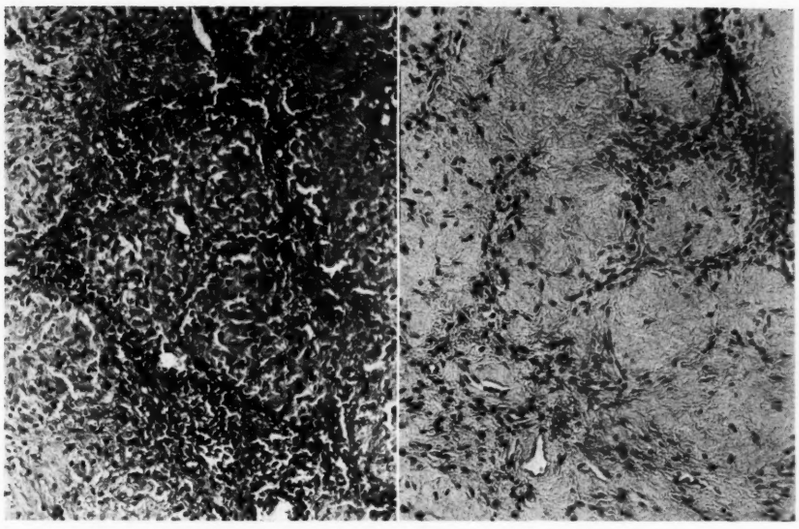
On admission physical examination revealed no peripheral lymphadenopathy. The Nickerson-Kveim test showed a positive reaction. An axillary lymph node subsequently became palpable and biopsy disclosed sarcoidosis. Some of the granulomas showed foci of hyalinization. The patient continued to feel well for almost three years. However, the mediastinal nodes slowly enlarged and in September, 1950, she noted an irregular swelling in the right submaxillary region which eventually made the jaw bulge. Examination showed a cluster of four cherry-sized nodes in that area. Two of these were excised for microscopic study and the other two were left behind. The excised nodes again showed sarcoidosis but no hyalinization was seen.

Cortisone was administered intramuscularly for forty days starting October 16, 1950. The patient received a daily dose of 150 mg. for the first week and 100 mg. thereafter or 4.5 gm. in all. In one week the two submaxillary nodes which had been left behind began to shrink and soften. In two weeks neither of them could be felt and they did not again become palpable. The mediastinal nodes on the other hand did not decrease in size.

The patient has been observed eight months following treatment. Three months after the drug was stopped a new node the size of a hazel nut appeared in the right posterior triangle of the neck. This has not changed in size.

Comment. Freshly enlarged peripheral lymph nodes promptly shrank under therapy but older mediastinal lymph nodes maintained their huge size. Therapy did not prevent appearance of a newly enlarged lymph node at another site three months later.

CASE IV. *Recent flareup with parotid and peripheral lymph node enlargement; regressing pulmonary and mediastinal lymph node involvement; quiescent uveitis.* I. C., a twenty-two year old Negro carpenter, was admitted to the Sarcoidosis Clinic of the Mount Sinai Hospital on May 16, 1950, with lung infiltrations and enlarged mediastinal lymph nodes found two weeks previously in a survey chest film. Six months before admission he had had an attack of parotid swelling which lasted two months. There had been low grade fever at that time. There were no ocular complaints. Physical examination on admission showed bilaterally palpable parotid glands of rubbery consistency.



3A 3B

FIG. 3. Case IV. A, photomicrograph (× 155) of a section of a cervical lymph node removed before cortisone therapy; large bland epithelioid cell granulomas stud the lymphoid substance. B, photomicrograph (× 155) of a section of an inguinal node removed after seventy days of cortisone therapy; dense, relatively acellular whorls of hyalinized connective tissue are seen. Two submental nodes removed one week later had a similar microscopic appearance.

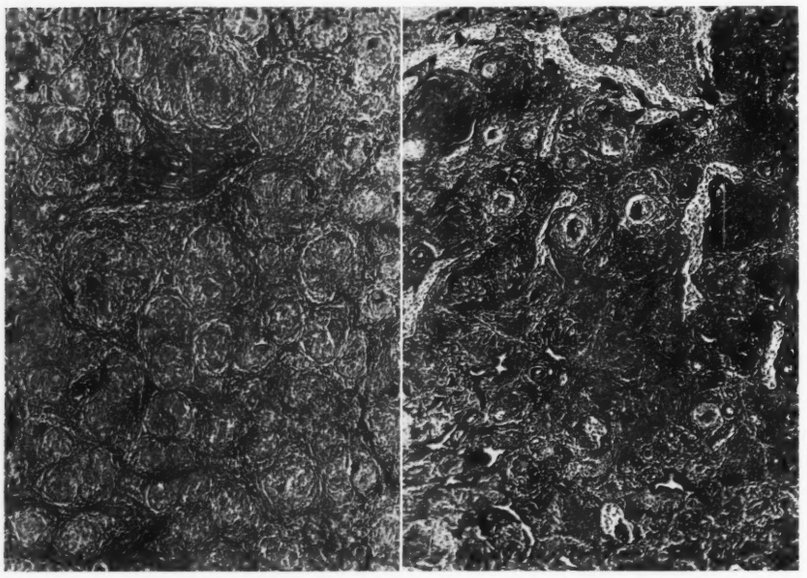
The glands were slightly enlarged, as were the posterior cervical lymph nodes.

Biopsy of one of the nodes on April 26, 1950, showed sarcoidosis. (Fig. 3A.) Some of the granulomas showed a few limited foci of hyalinization. Chest x-ray revealed fine nodular infiltrations throughout both lung fields and enlargement of the nodes in both hilar areas and in the right paratracheal region. The patient had mild uveitis in both eyes.

During the next six months the patient's condition improved spontaneously. The parotids became normal, the cervical lymph nodes shrank and the uveitis cleared considerably. The mediastinal lymphadenopathy diminished and the lung nodulation resorbed somewhat. But then, fairly suddenly, both parotids enlarged massively. At the same time the nodes in both inguinal regions, hitherto impalpable, became huge so that bulging masses the size of hen's eggs appeared in these areas. Each node measured 2 to 3 cm. in its longest diameter. Two cherry-sized nodes were now felt, also for the first time, in the right submental region. The cervical nodes had not enlarged again.

An eleven-week course of oral cortisone therapy was started December 12th. The patient received 150 mg. a day or 10.2 gm. in all. In one week the parotids decreased in size; in two weeks the lymph nodes in both the inguinal and submental regions began to shrink. This improvement continued until the twenty-fifth day when the patient was unable to appear for drug. He missed one week of therapy, then resumed it. During the lapse the parotid swelling promptly recurred and the glands regained their former size. The lymph nodes, however, did not flare up, and in the next two weeks, with therapy, the parotids again responded. Thereafter both nodes and glands declined until after eight weeks of treatment neither could be felt. On the seventieth day an inguinal node was excised and on the seventy-seventh day two small submental nodes were removed for histologic examination. These disclosed that the lymphoid substance had been extensively replaced by hyalinized connective tissue. (Fig. 3B.) Moreover, only a few small residual tuberculoid granulomas could be found in a careful search. The pulmonary lesions which had regressed before treatment cleared further under therapy and after one month were barely visible. The mediastinal lymph nodes also dwindled. The uveitis remained quiescent.

Comment. Enlarged parotids and lymph nodes shrank promptly; but when therapy was interrupted, the parotids at once enlarged anew. However, renewed treatment brought this under control again and improvement during



4A 4B

FIG. 4. Case V. A, photomicrograph (× 72) of a section of a femoral lymph node removed before cortisone therapy; non-caseating epithelioid cell tuberculoid granulomas completely replace the normal lymph node structure. Numerous giant cells of the Langhan's type are present. B, photomicrograph (× 72) of a section of a femoral lymph node removed after thirty-nine days of cortisone therapy; the epithelioid cell granulomas are no longer visible. There is now hyalinized connective tissue in whorls. The giant cells are prominent.

eleven weeks of therapy has been sustained for four and a half months.

CASE V. *Unilateral uveal involvement with blindness; progressive peripheral lymph node enlargement; pulmonary involvement; mediastinal lymph node enlargement; hepatosplenomegaly.* R. B., a twenty-five year old Negro housewife, was admitted to Montefiore Hospital on December 8, 1950, complaining of progressive loss of vision in her left eye. Examination eighteen months previously had revealed severe uveitis, peripheral lymphadenopathy with particular prominence of the femoral nodes and enlargement of the lymph nodes in the right paratracheal region. Biopsy of a supraclavicular lymph node in December, 1949, showed sarcoidosis.

Five months before admission a progressive nodular iritis had developed and, since standard therapy did not prove effective, the patient was referred to the hospital for cortisone therapy. On admission the right eye appeared normal. Vision of the left eye was reduced to seeing hand movements. The ocular tension was 11 mm. There was ciliary and episcleral injection. The pupil was irregularly oval and was covered by an opaque vascularized membrane which extended downward over the lower third of the iris and was attached to the posterior surface of the cornea. The upper half of the iris contained four grayish nodules. There were large keratic precipitates on the posterior surface of the cornea. The axillary and epitrochlear nodes were enlarged bilaterally. In both femoral regions clusters of enlarged nodes made the skin bulge. The nodes measured from 2 to 3.5 cm. in their longest diameters. Chest x-ray showed fine nodular and linear densities throughout both lung fields. The nodes of the right paratracheal region were enlarged. There was moderate hepatosplenomegaly.

Biopsy of a right femoral lymph node was performed on December 20, 1950. Several enlarged nodes belonging to the same chain were left behind. Microscopic section demonstrated complete replacement of the normal lymph node structure by numerous non-caseating granulomas composed of whorls of epithelioid cells and giant cells of the Langhans' type. None of the granulomas were hyalinized or sclerotic. (Fig. 4A.) A review of sections of the supraclavicular node removed one year earlier showed that they had an almost identical appearance.

The left eye was treated using local cortisone therapy for two weeks as a prelude to intra-

muscular administration. On December 21st two drops of a 1:4 dilution of cortisone were instilled hourly into the conjunctival sac. After two days the globe was less injected and the corneal opacities decreased in size and density. After one week one of the iritic nodules appeared smaller. The membrane over the iris appeared unchanged. At that time 0.4 cc. of cortisone was injected beneath the bulbar conjunctiva. During the next week the iritic nodules became smaller and some of the larger keratic precipitates disappeared.

Intramuscular cortisone was begun on January 4, 1951, and was continued for sixty-three days. The patient received 150 mg. a day for the first six weeks, then 100 mg. daily, or 8.5 gm. in all. The ocular lesions continued to regress and by the fourth week of intramuscular therapy all the iritic nodules had disappeared, leaving defects in pigmentation of the iris. Although the scar tissue membrane over the pupil lost its vascularization and became thin, its continued presence prevented any improvement in visual acuity. The axillary and epitrochlear lymph nodes shrank promptly and in two weeks were no longer palpable. The femoral nodes, which had been much larger than these, also waned, but their shrinkage required a period of five weeks. There was no significant change in the chest film taken six weeks after therapy was started but after nine weeks the nodular and linear densities cleared. However, the enlarged paratracheal node did not grow smaller. The hepatosplenomegaly remained unchanged. The serum globulin, which had been 4.1 gm. per cent at the start, dropped to 3.0 gm. per cent at completion of therapy. On the thirty-ninth day a lymph node measuring less than 1 cm. in diameter was removed from the right femoral region. This was from the same chain from which the pretreatment biopsy specimen was obtained. Microscopic section revealed a striking picture. (Fig. 4B.) There were now irregular whorls of dense hyaline connective tissue where the epithelioid cell granulomas had previously been seen. Giant cells, many of them vacuolated, were still present. Tubercles, as such, could not be found.

Five days after therapy was discontinued the patient showed signs of agitation and during the next three days an acute psychosis developed. This necessitated transfer to a psychiatric hospital where her mental symptoms cleared within two weeks. She was discharged after a three-and-a-half week stay without apparent psychic residua and subsequent examination during the next three months showed no relapse.

The peripheral lymph node enlargement did not return, nor did the iritic nodules. The eye showed reduced tension. The pulmonary fields showed a return of nodulation after six weeks and the chest film had the same appearance as the pretreatment film. The enlarged paratracheal nodes were still present unaltered four months after therapy, at which time the serum globulin rose to 3.8 gm. per cent.

Comment. The psychotic episode which began four days after a sixty-three-day course of cortisone happily proved to be rapidly self-limiting. Although marked regression was noted in the ocular lesions under local and systemic therapy, the patient's paramount complaint, loss of vision, has not been affected. An enucleation will probably have to be performed eventually. The peripheral lymph node shrinkage was prompt, yet the enlarged mediastinal nodes did not respond.

The most striking feature of this case is the complete hyaline replacement of the tuberculoid granulomas in the femoral lymph node after thirty-nine days' therapy. The nodes did not enlarge again during four months following treatment but the pulmonary lesion recurred in six weeks.

CASE VI. *Progressive dyspnea from long-standing pulmonary involvement; hilar lymph node enlargement.* M. K., a forty-seven year old white female dental assistant, became ill in November, 1946, with dyspnea on exertion, cough and persistent wheezing. Investigations for allergens proved unrevealing and she experienced little relief from bronchodilator drugs. In June, 1948, a chest film revealed many linear densities in both lung fields and enlargement of the hilar lymph nodes bilaterally. Hodgkin's disease was suspected and she received a course of radiation therapy to the chest, without improvement. The dyspnea grew worse in the next two and a half years; and when she was first seen in December, 1950, she could walk but a short distance without pausing for breath.

Examination revealed a chronically ill appearing woman. Her resting respiratory rate was 32 per minute. The breathing was labored and noisy. There was no peripheral lymphadenopathy. Coarse wheezes were heard over both sides of the chest.

A chest film showed linear densities in both

lung fields with enlargement of the hilar nodes bilaterally. Comparison with the chest film made in 1948 showed little change. The Nickerson-Kveim skin test showed a positive reaction. Bronchoscopy disclosed narrowing of the right lower lobe bronchus as if by extrinsic pressure. The mucosa throughout the bronchial tree appeared thin and atrophic. No biopsy was taken.

Intramuscular cortisone therapy was started January 25, 1951, and continued twenty-eight days. The patient received 100 to 150 mg. a day or 3.75 gm. in all. Within forty-eight hours the patient's cough and wheezing lessened and her resting respiratory rate fell to 18 per minute. In one week she could walk without halting for breath about four times as far as before taking the drug. Then, after twenty-eight days, she became disturbed by marked insomnia and increasing mental tension, and the drug had to be discontinued. The mental symptoms promptly abated. Chest x-ray at the end of the course revealed no significant change. The patient maintained her improved respiratory status for two months after cessation of therapy, at which time the dyspnea returned with its former severity.

Comment. There was prompt relief of dyspnea while the patient was receiving cortisone. In spite of the relatively short course relapse did not occur until two months after the course had to be interrupted.

CASE VII. *Unilateral uveal involvement with phthisis bulbi; progressive spinal cord involvement with ataxia and paraparesis of both lower extremities; peripheral lymphadenopathy; pulmonary reticulation.* L. H., a twenty-six year old Negro housewife, was admitted to the Mount Sinai Hospital on January 5, 1951. Her illness had started twenty months earlier (May, 1949) with progressive loss of vision in the left eye. She attended an eye clinic where a diagnosis of chronic uveitis was established. Chest film showed reticulation in both lung fields and a Nickerson-Kveim skin test was grossly positive. She received standard treatment with little improvement, and in the following six months the vision of the left eye deteriorated to the point where she could perceive only light.

In March, 1950, she began to stagger; this progressed so that she could not walk without falling to one side. There was some impairment of bladder control although she was not altogether incontinent. Her temperature reached 102°F. daily. In May, 1950, she was admitted to a hospital where examination revealed a diffuse lesion in the thoracic spinal cord. Spinal tap at that time showed high pressure, a slight increase of cells, high total protein, considerable reduction of the glucose concentration and normal chloride levels.

Cultures of the fluid for bacteria and higher organisms proved sterile. Serologic tests for syphilis were negative. The patient had given a history of successfully treated lues in 1946. In spite of the negative serologic findings and a negative tuberculin test she was empirically given 10,000,000 units of penicillin as well as 28 gm. of streptomycin in a two-week period, without effect upon the fever or the neurologic status.

The cervical lymph nodes became enlarged and biopsy, performed on June 26, 1950, showed sarcoidosis. There were a few minute hyaline deposits in the lymphoid substance. A diagnosis of central nervous system involvement by sarcoidosis was made.

The patient received an eleven-day course of ACTH, 100 mg. daily, without any change in the symptoms or findings. She was discharged from that hospital in July, 1950, and during the next six months she became chair-ridden. She continued to have fever but her general condition remained good. In January, 1951, she was referred to the Mount Sinai Hospital for cortisone therapy.

On admission examination showed large lymph nodes in both posterior cervical regions. The nodes were firm and the largest ones measured 2 cm. in their longest diameter. The left eye showed phthisis bulbi with complete loss of the anterior chamber. There was marked ciliary injection. The cornea contained numerous extensive opacities which were vascularized. The iris was also vascular and the pupil showed occlusion and seclusion.

Neurologic examination showed segmental involvement of the spinal cord from T_4 to T_{12}. The patient could barely support herself with two canes. The gait was ataxic with veering to the right. There were no signs of cerebellar involvement. Both lower extremities showed diminished position and vibratory sense. No suprapatellar reflexes could be elicited. Babinski reflexes were present bilaterally. The cerebrospinal fluid findings were as follows: Fluid was xanthochromic and clear; initial pressure, 220 mm.; final pressure, 180 mm.; 8 to 15 cells, mostly lymphocytes; glucose, 10 to 25 mg. per

cent; chlorides, 108 mEq.; total proteins, 100 to 160 mg. per cent; cultures and guinea pig inoculation for tuberculosis, negative; cultures for bacteria, fungi and viruses, negative. The chest film still showed reticulation in both lung fields.

Oral cortisone therapy was started January 30, 1951, and was continued for sixty-seven days. The patient received 7.0 gm. of drug; the daily dose was 150 mg. for the first ten days and 100 mg. for the rest of the course. In one week the patient was noted to have better balance while being weighed. She began to walk more steadily and three days later discarded one cane. She got in and out of a bathtub unassisted for the first time in nine months. In spite of this, neurologic examinations showed no significant changes and the fever persisted. During the third week the weakness of the lower extremities returned and her activities were again limited essentially to those of the pretreatment period.

The enlarged cervical lymph nodes became smaller by the tenth day and after one month were no longer palpable. A small cervical lymph node was removed one week after termination of the course, and this showed hyaline deposits in and around the tuberculoid granulomas. The hyalinization was more extensive than that seen in the sections of the lymph node removed seven months before treatment was started. There were still many epithelioid cell tubercles which were little altered from their pretreatment appearance.

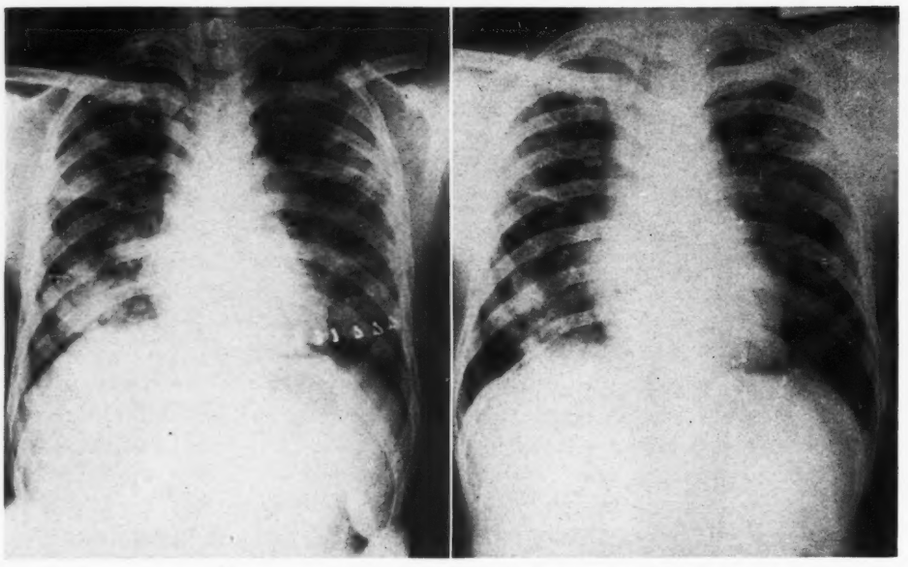
The affected eye showed little change during the course of therapy. Enucleation was performed eleven days after therapy was completed. Histologic section showed numerous tuberculoid granulomas surrounding the remains of the iris and involving the ciliary body. Some of these granulomas also showed partial fibrosis and hyalinization but for the most part the epithelioid cell structure was maintained. Occasional giant cells were visible. Throughout the course of therapy the patient continued to have fever, her temperature ranging from 100° to 102°F. daily. The chest films showed no alteration of the reticular pattern. The only significant change in the cerebrospinal fluid findings was a return to normal of the glucose concentration during the last two weeks of therapy. It rose from 10 to 25 mg. per cent to 45 to 50 mg. per cent. Serum globulin, which had been 3.8 gm. per cent at the beginning of therapy, never fell below that level throughout the course.

The patient was observed for three months following discontinuation of therapy. The neurologic status was unaltered. The lymph nodes had not enlarged again but fever persisted.

Comment. Destruction of the left eye had progressed so far that it is not surprising that cortisone failed to exert a beneficial effect. Sustained peripheral lymph node shrinkage is again encountered although histologically many residual epithelioid cell tubercles were present. Hyalinization appeared to exceed that which was present in the pretreatment biopsy. The histologic appearance of the granulomas in the enucleated eye was similar to that of the lymph nodes. The fever, for which no cause other than sarcoidosis could be found, failed to subside while the patient was receiving therapy. This brings up the question of whether dosage was adequate. The transitory improvement in the neurologic status remains unexplained. The patient achieved no significant gain from therapy.

CASE VIII. *Recent flareup of peripheral lymphadenopathy and spread of old cutaneous lesions.* M. B., a forty-four year old white attorney, entered the Mount Sinai Hospital on February 22, 1951, complaining of a swelling behind the left ear of three months' duration. About four years previously he had noted a similar swelling, in an adjacent area, that had persisted one year. At that time a biopsy had been performed with excision of an enlarged lymph node which on section revealed sarcoidosis. At that time, too, he had a small cutaneous lesion next to the inner canthus of the right eye. He was well until November, 1950, when the swelling in the left postauricular region recurred and the cutaneous lesion, which had remained unchanged for three years, grew larger and became crusted at its upper end. Examination on admission revealed many enlarged, firm lymph nodes in both cervical regions. At least eight could be palpated. They ranged from 2 to 4 cm. in their longest diameters. A nodular, erythematous area with raised edges was present over the bridge of the nose near the right eye. This measured 8 by 15 mm. On February 24, 1951, a left posterior cervical node and a portion of the cutaneous lesion were excised. Both showed noncaseating tuberculoid epithelioid cell granulomas without hyalinization.

Oral cortisone therapy was started on February 28th and was carried on for sixty-five days. The patient received a daily dose of 150 to



5A 5B

FIG. 5. Case IX. A, x-ray of chest before treatment with cortisone showing diffuse infiltrations in both lungs with enlarged mediastinal lymph nodes; the metal clips are in the skin. They were placed there after lung biopsy, performed two days earlier. B, x-ray of chest of same patient after five weeks' treatment with cortisone showing clearing of many of the infiltrations and some shrinkage of the mediastinal nodes; there is residual streaking in both lung fields.

175 mg. or 9.2 gm. in all. By the ninth day the cutaneous lesion appeared paler and its edges flatter. In two weeks all the enlarged lymph nodes became smaller. By the end of the sixth week the lymph nodes were no longer palpable. The cutaneous lesion continued to grow paler and flatter but it never entirely lost its erythema. The crusting disappeared.

The patient was observed for seven weeks following therapy. During the third week two lymph nodes in the cervical area became palpable again. They did not grow any larger in the next four weeks. The cutaneous lesion remained flat and pale and the crusting did not reappear.

Comment. Peripheral lymphadenopathy responded well to therapy but a mild relapse occurred after three weeks. A cutaneous lesion which had also regressed under therapy but had not entirely cleared showed no relapse seven weeks after therapy.

CASE IX. *Widespread pulmonary involvement; mediastinal lymphadenopathy.* T. M., a twenty-seven year old Negro glazier, was admitted to the Sarcoidosis Clinic of the Mount Sinai Hospital on October 6, 1950, because of abnormal findings in a chest survey film made in August, 1950. He had had a slight non-productive cough and dyspnea on exertion for two months. Chest films made in 1943 and 1945 had shown no abnormality. Physical examination on admission disclosed no significant findings. Chest films showed widespread, confluent infiltration in both lung fields. Interspersed among these were numerous fine and coarse nodular and linear densities. Both hilar and the right paratracheal lymph nodes were enlarged. (Fig. 5A.)

A Nickerson-Kveim test showed a positive reaction. For the next six months the pulmonary infiltrations extended and the mediastinal lymph nodes grew larger. Exploration of the right axilla yielded a small lymph node with normal histologic structure. A lung biopsy was therefore performed on April 4, 1951. Palpation of the lung revealed innumerable shot-like nodules. Microscopic section of a small wedge of excised lung showed many discrete and conglomerate epithelioid cell granulomas. A few nodules showed small areas of hyaline connective tissue. (Fig. 6A.)

Oral cortisone therapy was started April 11th and was continued seventy-three days. The patient received 150 mg. a day the first ten days and 100 mg. thereafter or 7.65 gm. in all. Cough and dyspnea subsided by the seventh day. Three days later the pulmonary infiltrations showed some resolution and the mediastinal lymph nodes appeared less prominent. Thereafter, chest films

6A 6B

FIG. 6. Case IX. A, photomicrograph (× 30) of biopsy from left upper lobe before cortisone therapy showing one large conglomerate epithelioid cell tuberculoid granuloma and numerous small ones in alveolar septa; these showed scattered areas of fibrosis and hyalinization not clearly visible here. B, photomicrograph (× 84) of biopsy of apical portion of left lower lobe after fifty-nine days of cortisone therapy; there is marked pulmonary fibrosis with hyalinization. Tuberculoid granulomas are present in fewer numbers and many appear atrophic.

showed continuing resorption and, after five weeks, marked clearing of many of the infiltrations, leaving a residue of scattered strands in both lung fields. (Fig. 5B.)

On the fifty-ninth day lung biopsy was again performed. On palpation of the lung there now appeared to be fewer nodules than were felt at the pretreatment thoracotomy. A firm noncrepitant area was found in the apex of the left lower lobe and a portion of this was excised. On microscopic section the lung showed extensive areas of fibrosis and hyalinization. The epithelioid cell tuberculoid granulomas were still present but were fewer in number. (Fig. 6B.) The serum globulin, which had been 4.2 gm. per cent, dropped to 2.4 gm. per cent.

Comment. The serial chest films showed prompt and continuous resolution of many of the infiltrations which had been spreading before treatment. Shrinkage of mediastinal lymph nodes under therapy was also prompt and continuous. Post-treatment lung biopsy appeared to show a decrease in extent of granulomatous involvement of the pulmonary tissue and an increase in the fibrosis and hyalinization. This was accompanied with marked fall in the serum globulin level.

CASE X. *Progressive dyspnea from pulmonary involvement; mediastinal and peripheral lymphadenopathy.* R. R., a twenty-nine year old white housewife, was admitted to the Sarcoidosis Clinic of the Mount Sinai Hospital on October 17, 1950. She complained of increasing dyspnea on exertion and non-productive cough that had lasted eighteen months. A chest x-ray made in August, 1950, had shown widespread pulmonary lesions. On examination the patient appeared to be chronically ill. She was dyspneic while talking. Her resting respiratory rate was 28 a minute. Moderately enlarged lymph nodes were palpable in both axillas and in the inguinal regions. Examination of the lungs showed diminished breath sounds bilaterally and inconstant wheezes. Chest x-ray revealed coarse linear and confluent nodular densities throughout both lung fields. There were numerous emphysematous bullae at both bases and the lung roots, which were somewhat prominent bilaterally, were drawn upward. A left axillary lymph node biopsy was performed on Novem-

ber 7, 1950, and on section showed sarcoidosis. Minute areas of hyalinization were present in the lymphoid substance and around some of the granulomas.

Cortisone therapy was started on April 24, 1951, and was continued forty-nine days. The patient received in all 6.3 gm., a daily dose of 100 to 150 mg. In one week the patient could climb three flights of stairs without discomfort whereas she had formerly had to pause for breath every half flight. This improved status was maintained throughout the period of therapy. After the second week the axillary and inguinal nodes shrank and were barely palpable at the end of four weeks. Chest x-rays showed no significant change. The serum globulin, which was 3.4 gm. per cent before treatment, was 3.8 mg. per cent at the end of the course.

The patient was observed for six weeks following therapy. After two weeks without drug she noted some return of dyspnea. A chest film taken at that time showed a slight increase in the infiltrations in the right lung. At the end of six weeks the patient's dyspnea grew worse and was only slightly less troublesome than before treatment began. The peripheral lymph nodes had not enlarged.

Comment. Extensive scarring and the presence of emphysematous bullae suggest that the pulmonary lesions were long-standing. As in Case VI, relief of dyspnea and cough was prompt and striking despite the absence of significant roentgenographic change. Symptomatic relapse occurred quickly once the drug was stopped.

CASE XI. *Suppurative bronchiectasis of right middle lobe secondary to endobronchial involvement with sarcoidosis; pulmonary involvement; regressive hilar node involvement; splenomegaly.* J. W., a forty year old white subway attendant, was admitted to the Mount Sinai Hospital on March 2, 1951. His illness had started one year previously with non-productive cough and occasional wheezing. A chest film made at that time had shown streaking and fine nodulations in both lung fields as well as enlargement of the hilar lymph nodes. He continued working until two months before admission when he became acutely ill with severe cough, persistent fever, night sweats, loss of weight and expectoration of large amounts of purulent sputum. On admission his temperature was 101.6°F. and his respiratory rate was 34 per minute. Diffuse lymphadenopathy involved the nodes of the posterior cervical axillary and inguinal regions. Diminished breath sounds with prolonged expiration and coarse moist rales were heard over the lower portions of the anterior and posterior surfaces of the right chest. The spleen was enlarged and could be felt three fingerbreadths below the costal margin. A chest film disclosed shrinkage and consolidation of the right middle lobe. In addition there were faint linear and nodular densities scattered throughout both lung fields and slight increase in the size of the left hilar shadow.

Comparison with a film made one year previously showed regression of the enlarged hilar lymph nodes but no change in the nodules and linear densities. The right middle lobe infiltration was not present on the earlier film.

Bronchoscopy performed on March 29, 1951, disclosed narrowing of the right middle lobe bronchial orifice by thickened folds of mucosa. Recurrent purulent secretions could be aspirated from the lumen. Biopsy of the bronchial wall showed several non-caseating epithelioid cell tubercles beneath the mucosa. Acid-fast stains were negative. Bronchoscopic biopsy was repeated one week later with the same microscopic findings. A bronchogram showed cylindric bronchiectasis of the right middle lobe. The rest of the bronchial tree appeared to be normal. An enlarged axillary lymph node removed on April 3, 1951, showed sarcoidosis. There were a few focal areas of hyalinization in the periphery of some of the granulomas and in the lymphoid tissue substance.

It was believed that the suppurative bronchiectasis of the right middle lobe was secondary to partial bronchostenosis resulting from involvement of the bronchial wall by sarcoidosis. Treatment was therefore first directed at controlling the bronchopulmonary infection. To this end, local and systemic antibiotic therapy in massive dosage was instituted for a six week period. The patient received penicillin, streptomycin, chloromycetin and gantrisin.

In addition he received eighteen intratracheal instillations of a mixture of penicillin and streptomycin. Under this regimen the average daily sputum volume dropped from 90 to 30 cc. However, the sputum was still purulent, the temperature remained elevated and the patient continued to lose weight.

During his seventh week in the hospital oral cortisone therapy was started (April 25, 1951) and this was continued sixty-three days. The patient received 8.0 gm. of drug. He was given

100 mg. a day for seventeen days and then, since the fever had not subsided, 150 mg. Within two days his temperature became normal and it remained so throughout the course except for occasional slight rises. Rales were no longer heard and the sputum volume dropped further. A chest film made on the tenth day showed some clearing of the infiltrations in the right middle lobe, and bronchoscopy after three weeks revealed a widely patent middle lobe orifice with only slight mucosal edema. A chest film made after five weeks of therapy showed that many of the nodular and linear densities in both lung fields had regressed. The right middle lobe infiltrations had cleared leaving some streaking. The slightly prominent left hilar shadow remained unchanged. Splenic enlargement persisted. The peripheral lymph nodes began to shrink in two weeks but they remained slightly palpable.

Biopsy of an axillary lymph node on the twenty-sixth day and of an inguinal node on the fifty-eighth day showed an increase in the amount of hyalinized connective tissue compared to what had been seen in pretreatment lymph node sections. However, many small epithelioid cell granulomas without hyaline or fibrotic change were still present. Bronchoscopic biopsy was also repeated on the sixtieth day and this showed one residual tubercle without hyalinization. The serum globulin level, which was 3.5 gm. per cent at the start, was 3.0 gm. at the end of cortisone therapy.

Fever recurred without pulmonary symptoms while dosage of cortisone was being tapered off. The patient was transferred to ACTH therapy for the following thirty days. Hyperglycemia and a diabetic type of glucose tolerance curve were present shortly after the initiation of ACTH therapy. These receded as the dose of ACTH was reduced.

Comment. This case presented a dilemma as far as treatment was concerned. In usual circumstances a lobectomy would have been performed for the suppurative bronchiectasis of the right middle lobe. In this instance, however, it was feared that the rigidity of the bronchial wall involved by sarcoidosis would prevent proper healing of the bronchial stump and lead to a bronchopleural fistula. On the other hand, there was some risk of spreading the bronchopulmonary infection with the use of cortisone. This risk seemed to be the lesser one. In order to minimize it antibiotics were continued while the cortisone was given and no spread of infection occurred. The right middle lobe bronchial orifice became patent during cortisone therapy although a bronchoscopic biopsy performed on the sixtieth day still showed a residual epithelioid cell tubercle. The nodular and linear densities in both lung fields regressed somewhat and the peripheral lymph nodes shrank but remained palpable. The splenomegaly was unaltered.

Case xii. *Bilateral uveal involvement with loss of vision; secondary glaucoma; recent cutaneous involvement.* S. S., a fifty-seven year old white housewife, was admitted to the Mount Sinai Hospital on February 2, 1951, with complaints of diminishing vision. Her vision had been lessening for eighteen months and in June, 1950, a diagnosis of bilateral iritis with secondary glaucoma was made. There was marked contraction of the visual fields. The patient had received cortisone in the form of eye drops and intramuscular injections from October to December, 1950, but the injections were given irregularly and in dosage never exceeding 50 mg. daily. On admission abnormal findings were limited to the eyes. Visual acuity in both eyes was so reduced that she could discern only hand movements. There were numerous keratic precipitates on the posterior surface of the cornea of the right eye and ciliary and episcleral injection bilaterally. Posterior synechiae were present. The vitreous was cloudy in both eyes. The ocular tension was elevated to 70 mm. in the right eye and 40 mm. in the left.

Cortisone drops in a 1:4 dilution were instilled into the conjunctival sacs hourly. Under this regimen the patient's ocular tension returned to normal in ten days. There was little improvement in vision. Some keratic precipitates persisted and the vitreous remained cloudy. In March, 1951, a slightly raised, firm cutaneous nodule measuring 3 by 7 mm. was noted below and medial to the inner canthus of the left eye.

The patient reported that the nodule had been enlarging during the preceding weeks. The lesion was excised in its entirety. On microscopic section it revealed sarcoidosis.

It was believed advisable to make another attempt to improve the patient's vision by means of systemic cortisone therapy and she was admitted to Montefiore Hospital on May 28, 1951. She received 100 to 150 mg. of drug a day for fifty-seven days, with a total dosage of 7.0 gm. At present the dosage is being gradually reduced.

The patient's vision improved rapidly. In one week she could walk about the wards unaided. In four weeks vision in the right eye, which had measured 15/200 before admission, increased to 15/30. Vision in the left eye improved less: from 15/300 to 15/200. Visual field studies showed extensive defects bilaterally, a result of the advanced glaucomatous changes. Ocular tension remained normal throughout therapy. The keratic precipitates in the right eye disappeared after ten days but the synechiae were not affected. After three weeks the vitreous became clear in both eyes so that shallow cupping and pallor of the discs, both resulting from antecedent glaucoma, could be seen more clearly.

Comment. In spite of the return of ocular tension to normal levels under cortisone drops vision had not improved. The keratic precipitates persisted and the vitreous remained cloudy. Systemic therapy cleared up both these manifestations with gain in vision. The changes brought about by the secondary glaucoma appear to be irreversible and further significant improvement in vision is not to be expected.

CASE XIII. *Scattered subcutaneous nodules increasing in size and number; peripheral lymphadenopathy.* E. E., a twenty-six year old white housewife, was first seen on April 20, 1951. Three months before that she had noted numerous scattered hard nodules beneath the skin of the abdomen. The nodules had been growing in size and number. They never became red or tender and there was no fever.

Examination revealed many firm nodules the size of hazel nuts and walnuts in the subcutaneous tissue of the abdomen and in both lumbar regions. Many of the nodules appeared in clusters. They were not attached to the overlying skin. The lymph nodes in both inguinal regions were firm and enlarged. The largest nodes measured about 3 cm. in their longest diameters. Physical examination revealed nothing else remarkable. The tuberculin test was negative in a 1:100 dilution and the serum proteins were present in normal concentrations. Serologic tests for syphilis were negative. Chest x-ray film disclosed no abnormality.

Biopsy of an abdominal subcutaneous nodule and of a right inguinal node had been performed on April 6, 1951. Both the abdominal nodule and the lymph node showed many noncaseating epithelioid cell tubercles studding the tissues. There were occasional giant cells of the Langhans' type. There were also large areas of fibrosis and hyalinization.

In the abdominal nodule there were several fairly extensive areas of necrosis. These areas were somewhat larger than those usually seen in sarcoidosis. Sections stained for acid-fast bacteria and spirochetes disclosed no organisms. Because the microscopic appearance of the lymph node was consistent with sarcoidosis and because of the negative tuberculin test and a Nickerson-Kveim test reaction which proved to be positive, the pathologist believed that sarcoidosis of the Darier-Roussy type was the most likely diagnosis.

Cortisone therapy was started June 1, 1951, and is still going forward. The patient has received 150 to 175 mg. daily for fifty-five days or 8.5 gm. in all. At the end of the second week the abdominal nodules felt somewhat softer and smaller. The lymph nodes in both inguinal regions also started to recede. Regression at both sites continued slowly and after six weeks the abdominal nodules were reduced to about half their pretreatment size. The lymph nodes had almost all receded but one node was still firm and measured about 2 cm. in its longest diameter.

On the forty-third day this node and a shrunken abdominal nodule were excised. Microscopic section revealed little change from what had been seen in the pretreatment biopsy. Areas of epithelioid cell granulomas persisted, many of them fibrotic and hyalinized, but no increase in the latter process could be discerned.

At present the abdominal nodules continue to shrink slowly. Therapy will be maintained at smaller dosage.

Comment. This is an unusual form of sarcoidosis involving the subcutaneous tissue and peripheral lymph nodes. Regression under therapy proceeded slowly and was only partial. In spite of shrinkage the subcutaneous nodules did not show significant histologic changes after six weeks of therapy. Since there was prompt relapse in Case II in which subcutaneous masses disappeared under therapy, it is intended to continue the drug at smaller dosage for an extended period.

COMMENTS

It would appear from this experience with thirteen patients that cortisone exerts a suppressive effect upon the lesions of sarcoidosis. This impression is reinforced by reports from others. Sones and his co-workers[2] used cortisone in two cases of sarcoidosis. In one case there were

cutaneous, ocular, pulmonary and lymph node lesions. Marked regression occurred at these sites after a fifteen-day course using 200 mg. of the drug daily.

Biopsies of a cutaneous lesion and a peripheral lymph node at the end of the course showed complete replacement of the sarcoid granulomas by non-specific inflammatory tissue. Chest films three months later showed no recurrence of pulmonary nodular lesions or mediastinal lymphadenopathy.

In the second case parotid and lacrimal gland enlargement, pulmonary nodulation and mediastinal node enlargement all promptly receded during an eleven-day course using 2 gm. of cortisone. Here a biopsy of the parotid gland after therapy revealed shrinkage of the granulomas and increase in fibrosis and hyalinization as compared with a pretreatment biopsy of the same tissue. No relapse occurred within the following three months.

Michael treated five cases of sarcoidosis with cortisone.[3] Three patients had completed courses of forty-one, forty-nine and fifty-one days, respectively. The other two were still receiving the drug. The dosage was 100 mg. a day. All patients had improved pulmonary function during therapy. Pulmonary shadows cleared in three or four weeks and peripheral lymph node enlargement receded within ten days to two weeks. Biopsy of peripheral nodes in two patients after three weeks of therapy showed fibrosis in one and fewer granulomas in the other. Pulmonary infiltrations recurred three weeks after therapy was stopped and in two patients appeared to be worse than before treatment.

One patient with extensive pulmonary infiltrations showed no change on repeated chest films but experienced marked relief of dyspnea and cough within one week. However, three weeks after the drug was discontinued the symptoms were as severe as before.

Meissner[4] observed the ocular lesions of two patients included in Michael's report. One with asymptomatic uveitis experienced clearing of keratic precipitates after one week. In the other patient vascularizing keratitis regressed in two days and chronic iridocyclitis improved substantially although not so quickly.

Engeleman and associates[5] reported a case of sarcoidosis with enlarging peripheral lymph nodes and bilaterally swollen epididymides. There had been pulmonary and mediastinal lymph node involvement also but these had regressed. Uveitis likewise had been present but was quiescent. The patient received a thirty-six-day course of treatment with a daily dose of 200 mg. There was prompt recession of the peripheral lymph nodes and the epididymides returned to normal size. Three lymph node biopsies were performed before therapy was started and all showed non-caseating tuberculoid granulomas without evidence of fibrosis or hyalinization. Biopsy was repeated after thirteen days of therapy and considerable fibrosis was found. Small tubercles were still fairly numerous. Another lymph node biopsy made after thirty-one days showed conversion of the tubercles into hyaline and fibrotic nodules. Only multinuclear giant cells remained. The serum globulin fell from 4.0 to 2.0 gm. per cent after treatment. Mild relapse occurred in eight weeks.

Straus[6] reported considerable clearing of pulmonary lesions and relief of dyspnea in a patient with sarcoidosis treated with 100 mg. a day. The pulmonary clearing took place within three weeks. When the report was made, the patient was still under treatment.

Galdston and co-workers[7] treated one sarcoidosis patient with ACTH for twenty-three days. The dosage was 80 mg. daily. There was fever, involvement of peripheral and mediastinal lymph nodes and cutaneous and subcutaneous tissue, and hepatosplenomegaly. The cutaneous and subcutaneous lesions regressed promptly and the fever fell. The enlarged mediastinal nodes and hepatosplenomegaly were unaltered. A Nickerson-Kveim papule also diminished. A tonsillar biopsy obtained after twenty days of treatment showed regression of sarcoid granulomas and replacement by fibrosis and hyalinization. The latter had not been present in sections of a pretreatment biopsy from the same area. Fever returned three days after the ACTH was withdrawn.

Thus a combined total of twenty-three patients with sarcoidosis have shown objective and subjective improvement of varying degree while under the influence of cortisone or ACTH. There is a tendency of the disease to relapse fairly promptly on withdrawal of the drug just as there is in other chronic diseases which respond. Relapse in sarcoidosis, however, is not invariable and this might be explained by the occurrence of natural remissions in the post-treatment period. When therapy stretches over a period of months, as it often did in the present study, the likelihood of encountering such remissions is increased.

Decisive evidence that the natural course of the disease is fundamentally affected by the drug is lacking; yet the repressive effect of the drug appears to be of value in reducing the activity of lesions and minimizing the damage to vital organs during exacerbations of the disease.

One may question the validity of attributing to cortisone the regressive changes found in biopsy specimens removed during therapy. Such are the natural variations in the histologic patterns of sarcoidosis with its frequently coexistent fresh and old lesions; the presence of regressive changes in specimens removed after treatment might be a matter of coincidence. One cannot know how representative isolated specimens are, but the repeated finding of later stages of healing in tissues removed during therapy than were present before makes it unlikely that chance is the only factor.

Sections of lymph nodes removed from different sites during therapy showed uniformity of regression in individual patients. In Case IV two submental lymph nodes and an inguinal node showed markedly increased hyalinization when compared with biopsy specimens removed before therapy, and in Case XI an inguinal and an axillary node both showed slight increase. It is not clear why some patients had marked hyalinization in post-treatment biopsies whereas others treated for the same period had only a slight degree of regression histologically.

In this series the favorable effect of the drug upon the peripheral lymph node lesions appeared to be more consistent and relapse occurred less often than at other sites of involvement. However, involvement of peripheral nodes is rarely a source of major disability to the patient. Eventually, spontaneous resolution without significant residua occurs.

It is otherwise with ocular and pulmonary lesions. Here, scarring which sometimes follows regression of the granulomatous lesions may produce severe, irreversible damage to the organ. Ocular lesions can produce loss of vision, as it did in four patients in this series. Lung lesions may lead to insufficiency of this organ. This occurred in two cases. Some of these cases with advanced involvement of eyes and lungs show how little can be gained from cortisone therapy when extensive scarring has already occurred.

The question comes up whether use of cortisone early, before scarring sets in, can prevent the crippling sequelae of sarcoidosis. The question will be answered only when more patients receive timely treatment. It is already apparent that the course of treatment will have to be long if benefits are to be reaped. For the present it would seem wise to use cortisone particularly in those cases in which the site and extent of involvement portends dire consequences to the patient.

SUMMARY

Cortisone* was administered to thirteen patients with sarcoidosis for periods of twenty-eight to 106 days.

Objective and subjective improvement of varying degree occurred in all patients. Fresh lesions appeared to be more responsive than older ones.

Of ten patients whose course of therapy has been terminated seven showed relapse.

Thirteen post-treatment biopsy specimens from eight patients were available for comparison with specimens removed prior to treatment. Ten specimens showed slight to marked regressive changes histologically.

Acknowledgment: The author wishes to acknowledge his gratitude to Drs. Samuel Gartner, Adolph Posner and Myer M. Medine of the Ophthalmologic Service, Montefiore Hospital, for their help in the study of Cases I, V and XII.

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* Cortisone used in this study was partly supplied by Merck and Co., Inc.

Joint and Skeletal Muscle Manifestations in Sarcoidosis*

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SARCOIDOSIS is generally regarded as a disseminated disease capable of involving any organ or tissue.[1] Nevertheless, scant attention has been directed toward the skeletal system apart from the adequately described osseous lesions which have been found in as high as 10 to 20 per cent of the cases.[2,3] Joint involvement in sarcoidosis has been denied by some[2,3] and considered merely coincidental by others. A careful search of the literature has revealed only six cases with arthritis associated with and attributed to sarcoidosis.[4–8] Furthermore, this review has disclosed only a few references to sarcoid of the skeletal muscles.[5,9–11]

During the past few months we have observed four patients with migratory polyarthritis resembling rheumatic fever or rheumatoid arthritis and with histologic evidence compatible with sarcoidosis. Non-caseating epithelioid granulomas of the sarcoid type were demonstrated by lymph node biopsy in one case and in three cases by striated muscle biopsy, performed during the course of an investigation undertaken despite the absence of clinical manifestations referable to the skeletal muscle. These cases are reported to draw attention (1) to the association of sarcoidosis and polyarthritis and (2) to the value of muscle biopsy as a diagnostic procedure in cases of suspected sarcoidosis without cutaneous or lymphoglandular lesions.

CASE REPORTS

CASE 1. G. P., a thirty-three year old white male, was admitted to the Veterans Administration Hospital, Dearborn, Michigan, on December 21, 1950, with a history of migratory joint pains of four weeks' duration. The pain, stiffness and swelling began simultaneously in both knees but were more severe in the left and then spread concurrently to the ankles, meanwhile partially subsiding in the knees.

A short time later an exacerbation occurred in the symptoms referable to the knees. During the present illness the patient lost 12 pounds of weight. Approximately six weeks prior to admission penicillin had been given by a private physician for the treatment of "sinusitis." There was no history of allergic reaction to the penicillin.

Physical examination on admission revealed a thin white male who appeared chronically ill. His blood pressure was 130/70, pulse 128 and temperature 99.2°F. The head and neck were normal, with no obvious evidence of foci of infection in the sinuses, teeth or tonsils. The lungs were clear and the heart was entirely negative. The liver and spleen were not palpable and no lymphadenopathy was found. The prostate was negative. Both ankles and both knees were reddened, swollen and tender with pain on motion but no limitation of movement. No effusion was detectable.

The original impression was acute rheumatic fever and the initial treatment consisted of bed rest and sodium salicylate, 8.0 to 12.0 gm. daily. Under this regimen the patient continued to run a low grade fever with no relief of his symptoms. A roentgenogram of the chest (Fig. 1) revealed bilateral hilar adenopathy consistent with sarcoidosis. Roentgenograms of ankles, knees, hands, thoracic spine and paranasal sinuses were all within normal limits. An intravenous pyelogram was normal. In view of the lack of response to salicylates and the findings in the chest roent-

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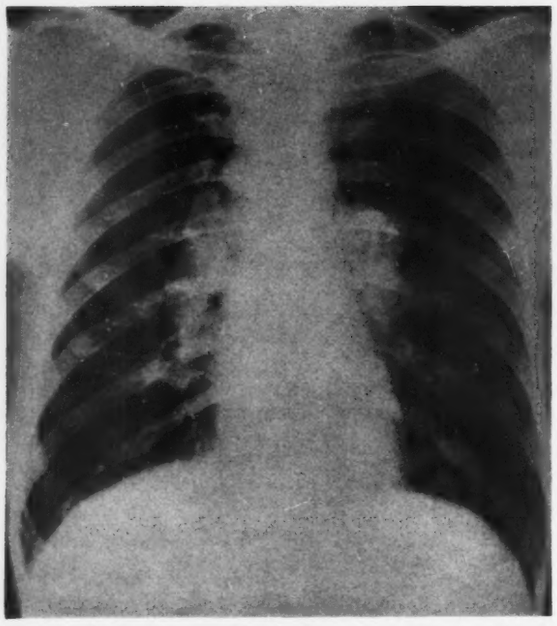

FIG. 1. Case I. X-ray of chest revealing bilateral hilar adenopathy.

genograms an extensive diagnostic work-up was initiated in order to investigate other causes of hilar adenopathy, fever and polyarthritis.

Repeated urinalyses were negative. The red blood count was 4,880,000/cu. mm.; hemoglobin varied from 11.5 to 13.5 gm. The white blood count ranged from 5,900 to 8,600/cu. mm. The differential count was as follows: Segmented neutrophils ranged from 45 to 72 per cent, juvenile neutrophils 0 to 14 per cent, lymphocytes 23 to 38 per cent, monocytes 1 to 11 per cent, eosinophils 0 to 2 per cent, basophils 0 to 1 per cent, hematocrit 37 to 43 per cent, platelet count was 259,000, and reticulocyte count 1.6 per cent. The bone marrow revealed monocytosis and eosinophilia but no evidence of granuloma. The sedimentation rate was 10 mm. an hour on admission and later rose to a maximum of 31 mm. an hour (Westergren method). The Paul-Bunnell test was negative. The blood Kahn test was negative. The serum protein, alkaline phosphatase, blood urea nitrogen, serum calcium, serum phosphate, cholesterol, cholesterol ester and bromsulfalein determinations were all found to be within normal limits. Completely negative results were obtained from agglutinations for Brucella abortus, typhoid, paratyphoid A and B and proteus OX19, repeated blood cultures, repeated sputum examinations for acid-fast organisms and gastric washings for acid-fast organisms, as well as stool examinations for occult blood, ova and parasites. Throat cultures revealed Streptococcus viridans and a few colonies of beta-hemolytic streptococci. The tuberculin, histoplasmin, coccidioidin and Frei skin tests were negative. Repeated electrocardiograms revealed notching of plateau of T waves in leads I and III.

The second and third weeks of hospitalization were characterized by an irregular septic type fever fluctuating between 98° and 101.6°F. Splenomegaly developed during the second week together with lymphadenopathy in the axillary and inguinal regions. The lymph nodes were of rubbery consistency, discrete, pea-sized and slightly tender. Biopsy of an inguinal lymph node obtained on January 5, 1951, revealed a reactive lymphoid and reticulum cell hyperplasia but no evidence of malignancy or granuloma. During the second and third weeks the joint symptoms gradually subsided and from the fourth week onward the joints were negative on physical examination. For the remainder of his stay in the hospital the patient ran an intermittent low grade fever. His general condition improved slowly but he continued to appear chronically ill. He complained of considerable fatigability but exhibited no specific symptoms or signs referable to the skeletal muscles.

A skin and muscle biopsy was taken at random from the right gastrocnemius muscle on February 8th. There was no local indication, however, to select this particular site for biopsy. Sections of skeletal muscle (Fig. 2) disclosed a large, noncaseating granulomatous nodule of the sarcoid type formed by epithelioid cells and Langhan's type of giant cells surrounded by an irregular but variable rim of lymphocytes. The muscle within the nodule was destroyed while the surrounding muscle showed early degenerative changes with loss of striation and displacement by the enlarging granuloma. The subcutaneous fat revealed a similar but smaller granuloma and there were focal lymphocytic infiltrations about the accessory skin structures. No organisms were found with routine hematoxylin and eosin, Giemsa, acid-fast and gram stains, nor were crystalline particles seen.

A flat plate of the abdomen made on February 15th revealed hepatomegaly and splenomegaly. These findings were confirmed by peritoneoscopy performed on March 2nd, at which time another skin biopsy and a liver biopsy were obtained. The biopsy of the liver (Fig. 3) contained noncaseating granulomas similar in appearance to

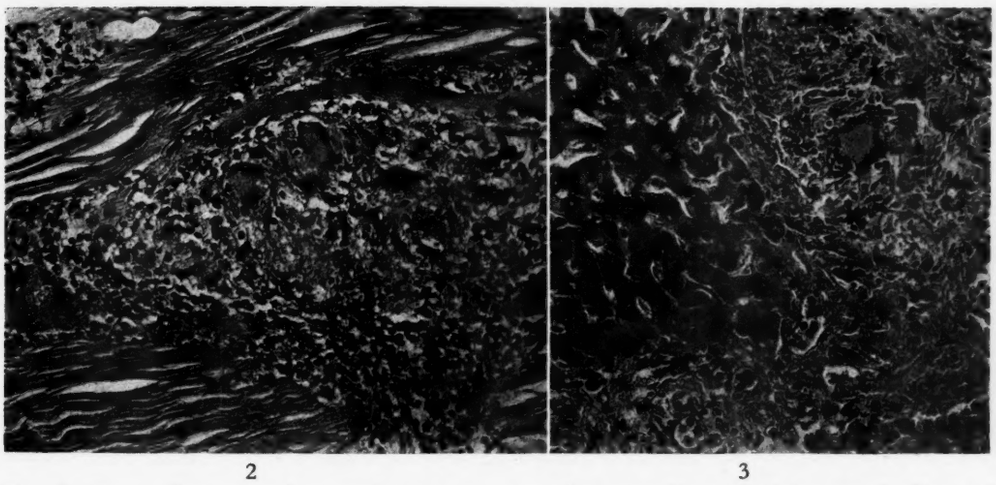

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FIG. 2. Case I. Gastrocnemius muscle; note non-caseating granuloma involving muscle fibers of Boeck's sarcoid type.
FIG. 3. Same case. Liver; revealing the edge of a non-caseating granuloma in the portal canal.

those found in the skeletal muscle and subcutaneous fat.

On March 6th a repeat muscle and skin biopsy was taken from another random site in the right gastrocnemius muscle as a further check on the dissemination of the lesions. The second biopsy of muscle revealed the same histologic picture as the first biopsy. The second skin biopsy was negative. Again, no organisms or foreign particles were found with the routine and special stains. There was no histologic evidence of fungi in any of the tissue specimens. Cultures made from the second muscle biopsy on Sabouraud's medium showed no growth. Inoculations of chick embryo with material obtained from the muscle biopsy were made but showed no evidence of any virus.

In view of the demonstration of epithelioid granulomas of the sarcoid type in liver, muscle and skin, and the exclusion of other possible etiologic factors, a final clinical diagnosis of generalized sarcoidosis was made at discharge on April 4th.

CASE II. C. L., a twenty-six year old white male, was admitted to the Veterans Administration Hospital, Dearborn, Michigan, on February 21, 1951, with a history of migratory joint pains of six weeks' duration involving the left hand, left wrist, both knees, both hips and both ankles. The pains in his ankles and knees were accompanied with slight but definite swelling. During this six-week period prior to hospitalization he consulted several physicians who told him he had "pus" in his urine and treated him with penicillin. The last dose of penicillin was received approximately one week before hospitalization. A few days prior to admission subcutaneous nodules appeared over both pretibial areas and a dry, non-productive cough developed.

The past history revealed that the patient had bilateral chorioretinitis since the age of sixteen. He was also aware of having had cervical lymphadenopathy between the ages of sixteen and twenty.

Physical examination on admission revealed a well developed and well nourished white male who did not appear acutely or chronically ill. His blood pressure was 110/70, pulse rate 90 and temperature 100.2°F. Fundoscopic examination revealed healed chorioretinitis bilaterally. The tongue was slightly coated and the oral pharynx slightly injected. The teeth revealed no foci of infection. The tonsils appeared normal. The lungs and heart were negative to physical examination. There was no lymphadenopathy, hepatomegaly or splenomegaly. There was no costovertebral angle tenderness. The prostate was negative on physical examination. Tender, purplish subcutaneous nodules were present in both pretibial areas. There was tenderness of both knees and ankles with a minimal effusion of the left knee and limitation of motion of this joint.

Laboratory findings were as follows: Repeated urinalyses showed a definite pyuria; culture of catheterized specimen revealed Aerobacter aerogenes and Escherichia coli. Blood urea nitrogen and urinary concentration tests were normal. Prostatic massage with urethral smear disclosed

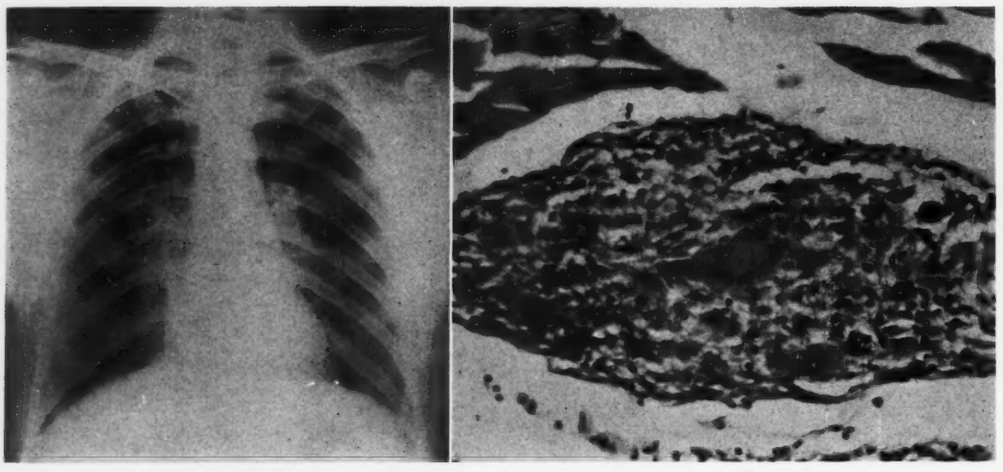

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FIG. 4. Case II. X-ray of chest showing bilateral hilar enlargement with a nodular, granular appearance in both lung fields.
FIG. 5. Same case. Gastrocnemius muscle; revealing non-caseous granuloma in endomysium.

no gonococci. The red blood count ranged from 4,080,000 to 4,910,000 and the hemoglobin from 12.5 to 16.0 gm. The white blood count ranged from 5,600 to 14,950/cu. mm. Repeated differential counts revealed the following: Filamented neutrophils ranged from 50 to 79 per cent, non-filamented neutrophils from 2 to 22 per cent, lymphocytes from 13 to 33 per cent, monocytes from 0 to 6 per cent, eosinophils from 0 to 5 per cent and basophils from 0 to 2 per cent. The sedimentation rate ranged between 20 and 47 mm. an hour. The Paul-Bunnell test was negative. The hematocrit ranged from 32 to 44 per cent and the platelet count was 222,040. The bone marrow showed monocytosis. No granulomas were found. The Kahn test was negative. The serum bilirubin and plasma proteins, including albumin-globulin ratio, were normal but the prothrombin concentration was 34 per cent. Completely negative results were obtained from agglutinations for Br. abortus, typhoid, paratyphoid A and B, and proteus OX19, repeated blood cultures, repeated sputum examinations and gastric washings for acid-fast organisms, and stool examinations for blood, ova and parasites.

The original impression was acute rheumatic fever and erythema nodosum. The initial treatment consisted of bed rest and sodium salicylate, 8.0 to 15.0 gm. daily. Under this regimen the patient continued to run a low grade fever with no relief of symptoms. A roentgenogram of the chest (Fig. 4) showed bilateral hilar enlargement with a nodular, granular appearance of both lung fields. Roentgenograms of both hands and the left knee were negative. An electrocardiogram was normal. The tuberculin and coccidioidin skin tests were negative but there was a positive reaction to histoplasmin.

Because of the clinical resemblance to Case I biopsy of skin and muscle was obtained. Since there were no symptoms or signs of muscular involvement, the specimen was taken at random from the right gastrocnemius area. In the endomysial connective tissue a non-caseating granulomatous nodule composed of epithelioid cells and a Langhan's giant cell was found and was compatible with sarcoid. (Fig. 5.) No fungi or other organisms were found.

The patient ran an irregular fever ranging from 99.0° to 102.4°F. for the first two weeks of hospitalization with defervescence by lysis during the third week. The erythema nodosum gradually spread upward to involve the thighs and then slowly faded. During the third and fourth weeks the joint symptoms gradually subsided. The patient was discharged from the hospital on March 29th after being asymptomatic for over a week, with a final clinical diagnosis of sarcoidosis with erythema nodosum.

CASE III. R. M., a twenty-eight year old colored female, entered Detroit Receiving Hospital on December 26, 1950, with a three-week history of migratory polyarthritis involving successively both knees, both ankles, the right ring finger and finally both wrists. Heat, swelling, pain and tenderness were described. The patient felt feverish and noted increased sweating. An evening temperature of 100°F. was reported by her physician. During the week

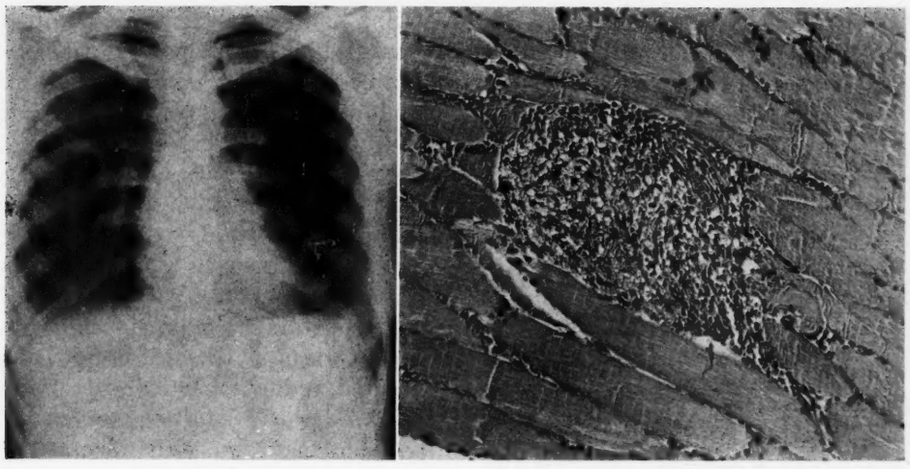

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FIG. 6. Case III. X-ray of chest showing enlarged hilar lymph nodes and diffuse reticulations throughout both lung fields.
FIG. 7. Same case. Gastrocnemius muscle; epithelioid granuloma in endomysium.

prior to admission painful subcutaneous nodules were noted in both legs, over the left ankle and the right knee.

Physical examination on admission revealed a well nourished, well developed individual who had a temperature of 101.8°F. but did not appear acutely ill. There were moderate swelling, heat, tenderness and some stiffness of both knees, ankles, left wrist and right ring finger. There were tender, round, red nodules about 1.0 cm. in diameter in the skin over both internal malleoli and the right knee. There was no obvious evidence of foci of infection in the tonsils, teeth or sinuses. Sticky rales, which did not clear on coughing, were heard at both lung bases. No adenopathy, hepatomegaly or splenomegaly was detected. Pelvic examination was negative.

All urinalyses were negative. The red blood count was 4,700,000/cu. mm. and the hemoglobin ranged from 10.5 to 13.5 gm. Repeated white blood counts ranged between 3,950 and 5,600/cu. mm. Repeated differential counts revealed filamented neutrophils ranging from 42 to 58 per cent, non-filamented neutrophils 8 to 20 per cent, lymphocytes 24 to 27 per cent, monocytes 7 to 8 per cent, eosinophils 2 to 4 per cent and basophils 1 per cent; hematocrit was 44 per cent, platelet count 130,000 and reticulocytes 5 per cent. The sedimentation rates were repeatedly around 30 mm. per hour (Westergren method). Preparation for sickling was negative after twenty-four hours. Bone marrow studies showed no diagnostic pattern; no granulomas were seen; lupus erythematosus cells were not present. Agglutinations, including those for Br. abortus, typhoid and paratyphoid A and B, did not show any significant elevation in titer. Tuberculin, coccidioidin and histoplasmin skin tests were negative. The Frei test was also negative. Five successive blood cultures revealed no growth after thirty days. Roentgenograms of chest (Fig. 6) on two occasions showed enlarged hilar lymph nodes and diffuse reticulation throughout both lung fields, consistent with sarcoidosis. X-rays of hands and feet showed no abnormalities. No periarticular swelling was seen. Electrocardiogram was within normal limits.

Despite salicylates in doses of 8.0 to 12.0 gm. per day pain, swelling and heat of joints continued in migratory fashion until several days before discharge. On admission the patient's temperature was 101.8°F. and fluctuated between 99.6 and 101.8°F. During the first week in January a new crop of raised, painful, well circumscribed nodules about 1.0 cm. in diameter appeared over both legs and were identified as erythema nodosum. This diagnosis was confirmed by the biopsy of one of these nodules. Eight days later the nodules had disappeared leaving darkly pigmented residua.

Shortly after discharge on January 12, 1951, migratory joint pains with heat, stiffness and swelling recurred and once again response to salicylates was indifferent. At this time both eyes became injected and the patient was referred to the Ophthalmological Clinic where slit-lamp examination showed many small granulomatous, white and pigmented keratotic

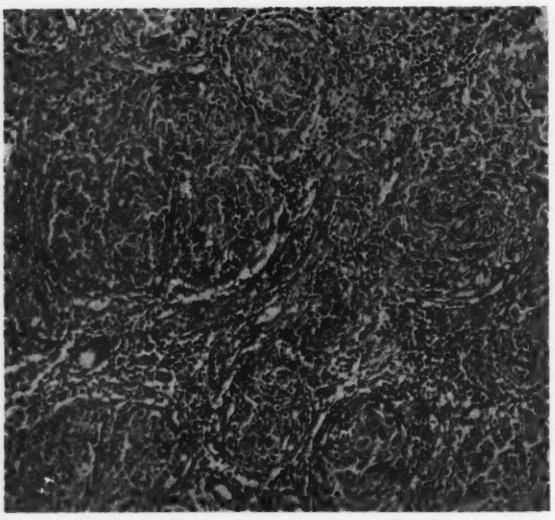

FIG. 8. Case IV. Right posterior auricular lymph node revealing epithelioid granulomas.

precipitates. A flare and cells were noted in the anterior chambers of both eyes. This type of uveitis was compatible with the diagnosis of Boeck's sarcoid. No involvement of the lacrimal or salivary glands was observed at this time.

A total of 0.4 cc. of cortisone (25 mg. per cc.) was injected subconjunctivally in both eyes with marked improvement of conjunctival injection. Eight hours later all joint symptoms disappeared and have not recurred to date. Subsequent examination revealed fading of the uveitis.

As the result of our experience with Cases I and II, the patient was recalled to the hospital for a muscle biopsy on March 21st. A specimen taken at random from the right gastrocnemius muscle (Fig. 7) revealed a non-caseating granuloma composed of epithelioid cells, a few giant cells of Langhan's type and a few lymphocytes, findings compatible with sarcoidosis. There was destruction of the muscle fibers previously occupying the position of the nodule. Bilateral painless parotid swelling developed subsequent to the biopsy.

CASE IV. C. M., a twenty-six year old colored female, entered Detroit Receiving Hospital on January 25, 1950, with the chief complaint of migratory polyarthritis of two weeks' duration, involving successively both knees, both ankles and the proximal joints of the right hand. Involved joints were described as hot, swollen and tender. At about the same time the patient became aware of painless "lumps" behind both ears and in both groins. She simultaneously noted tender nodules in the skin of both legs and arms. She was aware of fever but denied chills.

She had been hospitalized from February to April, 1949, for polyarthritis and painful nodules under the skin of her arms and legs, chills and fever. She was told at this time that she had rheumatic fever without involvement of the heart. Past history was not otherwise contributory.

Salient findings of the admission physical examination were temperature of 99.6°F., fusiform, hot swelling and tenderness of the proximal phalanges of the middle and ring fingers of the right hand, slight swelling, heat and tenderness of knees and ankles, and indurated, reddened, tender subcutaneous nodules in both legs. In addition, there was widespread lymphadenopathy with firm, non-tender, rubbery glands up to 1.0 to 2.0 cm. in diameter in the postauricular, anterior cervical, submaxillary and inguinal areas. Examination of the heart showed no abnormalities except faint mitral and aortic systolic murmurs which were thought to be functional. Liver and spleen were not felt.

Repeated urinalyses were negative. The red blood count was 3,960,000 to 4,060,000/cu. mm.; hemoglobin ranged from 9.5 to 11.0 gm. White blood count ranged from 3,550 to 6,600/cu. mm. Differential count revealed filamented neutrophils 47 to 65 per cent, non-filamented neutrophils from 4 to 9 per cent, lymphocytes from 19 to 28 per cent, monocytes from 0 to 6 per cent, eosinophils from 2 to 13 per cent, basophils 4 per cent, myelocytes 0 to 3 per cent, platelet count 243,000 and reticulocytes 0.7 per cent. Sedimentation rates were persistently elevated, all being above 50 mm. in one hour (Westergren method).

Examination of the bone marrow revealed no diagnostic pattern. There was a moderate reactive myeloid hyperplasia consistent with acute infection or inflammation. *In vitro* test for lupus erythematosus cells was negative. The serum total protein was 8.2 gm./100 ml. (albumin 3.8, globulin 4.4 gm.). Roentgenograms of chest showed hilar adenopathy but no parenchymal infiltration. These findings were consistent with but not diagnostic of Boeck's sarcoid. X-ray of the hands showed no changes except for soft tissue swelling. Electrocardiograms were negative.

Biopsy of the right posterior auricular lymph node disclosed a non-caseating epithelioid granulomatous inflammation (Fig. 8) consistent with sarcoidosis. An acid-fast stain of the involved gland was negative.

In order to investigate the possible etiology of this non-specific granuloma a series of tests was performed: Intracutaneous tuberculin 1:100, Frei test, coccidioidin skin test and histoplasmin skin tests were all negative. Heterophil agglutinations were negative in significant titers. Agglutinations, including those for Br. abortus, typhoid and paratyphoid A and B, were likewise not significantly elevated. Repeated gastric washings for the tubercle bacillus were negative. Kahn and Kolmer tests were all positive. The quantitative Kahn test showed 200 units. Spinal fluid was entirely negative.

A multiple diagnosis of rheumatic fever, erythema nodosum and a granulomatous lesion of sarcoid type was made. The patient was placed on intensive therapy with salicylates, with prompt response of joint swellings, heat and pain, and disappearance of the low grade fever. Consideration was given to the possibility that syphilis might be responsible for the lymphadenopathy; however, a total of 9,000,000 units of penicillin did not appreciably alter the size of the glands although the quantitative Kahn titer dropped from 200 K.U. to 10 K.U. within six months. It was finally concluded that the lymphadenopathy was independent of the syphilis.

Two months after discharge on March 2nd joint pains of migratory character recurred and involved the patient's knees, wrists, right elbow and small joints of the right hand in succession. She noted increasing weakness, weight loss (20 pounds), feverishness and sweats. Glands, although still painless, became larger and more widely distributed.

She was readmitted to Detroit Receiving Hospital on September 7th appearing chronically ill and showing weight loss. The right knee and wrist were hot, swollen and tender, and demonstrated some stiffness with limitation of motion. There were hot, tender, fusiform swellings of proximal joints of the right hand. The right elbow was stiff but not swollen.

Enlarged, firm, rubbery, discrete glands 1.0 to 2.0 cm. in diameter were now found in the posterior and anterior cervical chains, axillas, groins and epitrochlear regions. They appeared larger and more extensive than during any previous admission. As before, faint mitral and aortic systolic murmurs were detectable. The spleen was not felt. The remaining physical findings were within normal limits.

All previous laboratory studies, including chest x-ray, were repeated with almost identical results and only the outstanding ones are listed. Total protein was 9.2 gm./100 ml. (albumin 5.2 and globulin 4.0 gm.). Biopsies of postauricular and antecubital nodes again showed non-caseating granuloma of sarcoid type. In addition there was no growth in five blood cultures for Br. abortus.

Response of joints and pyrexia to salicylates was less prompt and there was residual stiffness and deformity. A therapeutic trial of streptomycin (1 gm. daily) was given for thirty days without any reduction in the size of the lymph nodes. The patient was discharged on December 3, 1950, with some slight residual deformity.

COMMENTS

Summary of Clinical Findings. The four patients reported in this communication exhibited the following manifestations in common: (1) migratory febrile polyarthritis resembling rheumatic fever but refractory to salicylates; (2) hilar lymphadenopathy consistent with Boeck's sarcoid; and (3) non-caseating epithelioid granulomas of sarcoid type, demonstrated by muscle biopsy in three and by lymph node biopsy in one. In addition, erythema nodosum was present in three patients, finely nodular pulmonary infiltrations in two, generalized lymphadenopathy in two, healed chorioretinitis in one and acute uveitis and parotitis in one patient.

Nature of the Histologic Lesion. Although the microscopic findings were compatible with sarcoidosis in each of the four cases, it was necessary to investigate other possible causes of the sarcoid type of altered tissue reactivity. Tuberculosis was excluded by the absence of caseation, the inability to demonstrate tubercle bacilli and the negative tuberculin test in each of the four cases. Syphilis was demonstrated serologically in one patient (Case IV) but was dismissed as a possible factor in the clinical manifestations after the lymphadenopathy proved refractory to a total of 9,000,000 units of penicillin. Brucellosis was investigated in all four cases by agglutination reactions and blood cultures on appropriate media in an atmosphere of 10 per cent carbon dioxide but was not demonstrated in any case. A search for fungi in all biopsy material proved fruitless; skin tests were negative for coccidioidomycosis in all cases and for histoplasmosis in three of the four patients. The Frei test was negative in all patients. Chicken embryo inoculations of biopsy material were negative

for viruses in the one case tested. Hodgkin's disease was excluded histologically. Trichinosis was excluded by the absence of eosinophils from the granulomas and the failure to find larvae on serial sections through the lesions.

In view of the polyarthritis the question arose as to whether the sarcoid-like lesions were really a manifestation of rheumatic fever or rheumatoid arthritis. The infiltration of the skeletal muscles described in rheumatoid arthritis and rheumatic fever is composed primarily of lymphocytes, plasma cells and a very occasional mast cell,[12–15] and is non-granulomatous. Thus it would appear that neither rheumatic fever nor rheumatoid arthritis could account for the granulomas found in the muscle, skin and liver of Case I, the muscle of Cases II and III and the lymph nodes of Case IV.

The suspicion of Felty's syndrome was aroused by the lymphadenopathy in Case IV. This was discarded because the histologic findings in the reported cases revealed infiltrations consisting of non-granulomatous perivascular collections of lymphocytes.[16–19]

Consideration was also given to the possibility that all features might be fitted into the syndrome of erythema nodosum inasmuch as typical skin lesions were present in three cases and compatible hilar adenopathy[20] was found in all four cases. A search of the literature disclosed two cases in which sarcoid-like granulomas were demonstrated by skin biopsy in erythema nodosum.[21] Unfortunately the report does not include a photomicrograph or a detailed description of the histologic findings to substantiate the diagnosis of sarcoidosis. The relationship between the roentgenologic findings in erythema nodosum and sarcoidosis has received further comment in additional cases not supported by histologic evidence of sarcoid.[22,23] On the other hand, the presence of sarcoid-like granulomas in erythema nodosum has been refuted by others.[20,24] The granulomatous infiltration of the liver demonstrated in Case I and the acute uveitis and parotitis in Case III could not readily be explained by a diagnosis of erythema nodosum. Therefore the erythema nodosum in these cases was regarded not as the primary entity but rather as a secondary manifestation. In this connection it is noteworthy that erythema nodosum has been included as an authenticated manifestation of sarcoidosis in a recent comprehensive review of this disease.[7]

The possibility of disseminated lupus erythematosus also received consideration in Cases III and IV but was made unlikely by the repeatedly negative urinalyses and the failure to demonstrate nucleophagocytosis in the *in vitro* test of Hargraves[25] and was dismissed after the biopsy material was studied.

It was also necessary to consider the possibility of an allergic origin, particularly in Cases I and II in view of the history of penicillin administration and the slight eosinophilia. The granulomas could be distinguished from those recently described[26] as allergic granulomas by the absence of a central core of eosinophilic necrosis, severe fibrinoid collagen change and the absence of eosinophils and of a radial arrangement of the macrophages. The absence of refractile and anisotropic crystalline foreign material in any of the granulomas excluded the possibility of post-traumatic subcutaneous granulomas.

Thus a diagnosis of sarcoidosis was made in all four cases from the presence of non-caseating epithelioid granulomas containing Langhan's giant cells after exclusion of other etiologic possibilities.

Skeletal muscle lesions have been reported in sarcoidosis[5,9,10] but have received scant attention, perhaps because of the rarity of clinical manifestations. It is therefore noteworthy that typical granulomas were readily demonstrated in routine muscle biopsies obtained at random in three cases in the absence of localizing symptoms and signs. If further experience substantiates the apparent frequency of asymptomatic muscle involvement, random muscle biopsy will constitute a valuable adjunct for the establishment of the diagnosis, particularly when no cutaneous or lymphoglandular lesions are detectable.

Migratory polyarthritis manifested by fever, pain, swelling and usually rubor and calor, resembling rheumatic fever, was observed in all four cases and was refractory to salicylates but gradually subsided to leave few or no residual deformities. These joint changes were not accompanied with roentgenologic evidence of osseous sarcoidosis. Although six cases of polyarthritis accompanying sarcoidosis have been reported,[4,8] the impression still prevails that the association is merely coincidental.[1,27] However, the occurrence of three distinct attacks of associated polyarthritis and granulomatous lymphadenopathy in Case IV and the development of uveal sarcoidosis simultaneously with an exacerbation of polyarthritis in Case III seem

beyond the realm of coincidence. From the clinical evolution in our cases it was concluded that the polyarthritis was a manifestation of sarcoidosis rather than due to an independent but simultaneously occurring disease.

SUMMARY

Four cases of sarcoidosis in which the diagnosis was established by demonstration of non-caseating epithelioid granulomas by muscle or lymph node biopsy are reported.

These cases illustrate the following manifestations hitherto regarded as rare or coincidental: (1) migratory febrile polyarthritis, resembling rheumatic fever, which was refractory to salicylates but gradually subsided to leave little or no deformity; (2) asymptomatic granulomatous infiltration of striated muscle. Erythema nodosum was present in three cases. Pronounced hilar lymphadenopathy consistent with either sarcoidosis or erythema nodosum was demonstrable in all patients and was accompanied with finely nodular pulmonary infiltration in two and generalized lymphadenopathy in two. Healed chorioretinitis was found in one patient and acute uveitis and parotitis in another.

The results of this study suggest that random muscle biopsy may constitute a valuable adjunct for the establishment of the diagnosis of sarcoidosis, particularly in patients without cutaneous lesions or significant lymphadenopathy.

Acknowledgment: The authors gratefully acknowledge the assistance rendered this study by Dr. O. A. Brines. Illustrations were prepared by the Medical Illustration Department of Veterans Administration Hospital, Dearborn, Mich.

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The Effect of Cortisone in Hodgkin's Disease*

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OBSERVATIONS of the effects of adrenal-cortical activity on mesenchymal tissues suggested the possibility of influencing the course of Hodgkin's disease by the administration of adrenal-cortical steroids or ACTH. It was shown by Dougherty and White[1] that adrenal-cortical substance effected involution of normal lymph nodes. Heilman and Kendall[2] produced regression of a lymph tumor in mice by the administration of cortisone. Dobriner et al.[3] found in the urine of patients with lymphoid neoplasms, as well as other malignant lesions, abnormally high concentrations of 11-hydroxy-etiocholanolone, a compound of adrenal-cortical origin. The excretion of other adrenal-cortical and gonadal steroid metabolites was markedly diminished. Depression of regeneration of mesenchymal tissues in rabbits treated with cortisone and ACTH was noted by Ragan et al.[4] Similar findings in mice were observed by Spain et al.[5]

It was demonstrated by Dalton and Selye[6] that marked eosinopenia accompanied the alarm reaction. This effect was shown to occur in man following administration of ACTH.[7] Since Hodgkin's disease is accompanied not infrequently with eosinophilia both in the peripheral blood and in involved tissue, this provides an additional if tenuous rationale for the use of adrenal steroids in Hodgkin's disease. In addition early favorable reports on the use of cortisone and ACTH in the treatment of such allied disorders as the leukemias made the trial of these agents in Hodgkin's disease essential.

Pearson et al.[8] found significant regression of lymphomas, including one case of Hodgkin's disease treated with cortisone. Bonner[9] treated a nineteen year old male with Hodgkin's disease with cerebellar involvement using 50 mg. of ACTH daily for thirty days. Questionable improvement was noted. There was no regression in the size of the spleen. Immediately following ACTH the patient relapsed into another acute phase of Hodgkin's disease. Three patients with Hodgkin's disease were treated with cortisone by Stickney, Heck and Watkins.[11] The spleen and lymph nodes of all three patients regressed but in fifteen to thirty days all beneficial effects were gone. Second courses produced similar results. Subsequent roentgen therapy was more effective than was cortisone. These observers found no significant changes in the blood. Biopsy specimens before and after treatment disclosed no significant alterations. Taylor et al.[12] reported on three patients with Hodgkin's disease treated with ACTH, one of whom also received cortisone. All showed major regression in the size of the tumor which was temporary.

This report comprises observation on ten patients with Hodgkin's disease treated with cortisone. Only patients who were acutely ill and had evidence of active progressive disease were selected in order to evaluate better the results of therapy. Manifestations of activity included fever, weakness, weight loss, increasing lymphadenopathy and hepatosplenomegaly or other organ involvement. The diagnosis in all cases was established by biopsy. No patients were selected who had had other forms of treatment in the month prior to institution of cortisone; most had far advanced disease and thus represented a severe challenge to the drug.

METHODS

Eosinophil counts were performed according to the modification by Forsham et al.[13] of the direct method of Dunger. Frequently a second count was performed on the same day four hours following the subcutaneous administration of 0.5 mg. epinephrine (Thorn test[7]). Plasma sodium and potassium concentrations were

* From the Medical Service and Radio-Isotope Unit of the Veterans Administration Hospital, Bronx, New York. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

determined by flame photometry utilizing an internally standardized instrument. Serum chlorides were determined by the method of Franko and Klein[14] and serum CO_2 combining power by the method of Van Slyke and Cullen.[15] Urinary excretion of 17-ketosteroids was estimated according to the method of Drektor et al.[16] The uptake of radioiodine, I^{131}, by the thyroid gland was determined by direct measurement over the neck twenty-four hours after an orally ingested dose of 50 microcuries I^{131}, carrier-free, utilizing a procedure previously standardized by the Radio-Isotope Unit of the Veterans Administration Hospital, Bronx, New York.[17]

Total body potassium was determined by the *in vivo* dilution technic with radiopotassium, K^{42}. Eighteen hours following the intravenous injection of approximately 100 microcuries of K^{42} with 20 mg. stable, carrier potassium, the radioactivity and stable potassium content of two urine samples were obtained at half-hour intervals for independent determinations, the results of which were averaged. The details of isotope counting are to be reported elsewhere. The total body potassium was calculated from the following formula:

$$\text{Total body K in mEq.} = \text{Activity of } K^{42} \text{ retained} \times \frac{\text{stable potassium in mEq./ml.}}{\text{activity of } K^{42}/\text{ml.}}$$

The K^{42} retained is taken as that injected less that excreted in the urine up to the time of the determination since normally only minute amounts are lost in the feces and sweat. This method measures approximately 95 per cent of the total exchangeable body potassium. The remaining 5 per cent is not accounted for owing chiefly to the slow rate of potassium exchange by the red blood cell mass which does not reach equilibrium with the remaining body tissues until about seventy-two hours. Similar determinations have been reported by Corsa et al.[18] Our studies in a larger series than is reported here confirm their conclusions with regard to technics and results in the determination of total body potassium.

Blood volume studies were performed with P^{32} tagged red blood cells using the isotope dilution technic.[19] Liquid sample–counting methods were used, the details of which are to be published elsewhere.

In vitro tests of the effects of cortisone on biopsy material of Hodgkin's nodes grown in tissue culture were also performed.*

Bone marrow examinations were made on "particle" smear preparations by a method previously described.[20] They were performed before therapy and at weekly intervals during the initial three weeks of treatment and thereafter at monthly intervals.

All patients had biopsies before therapy. Seven were classified as Hodgkin's granuloma, two as Hodgkin's sarcoma and one was unclassified. One patient had a subsequent biopsy while under therapy.

Mode of Administration. Initially patients were treated with 100 mg. of cortisone daily for three weeks. Patients who improved on this dosage over the period were then placed on 100 mg. three times weekly. This soon proved impracticable as all patients relapsed with the lowered dosage. For subsequent courses as well as for new patients treated later 200 mg. of cortisone daily were administered. This was continued for three to four weeks and resumed if relapse occurred on cessation of therapy. The drug was discontinued if patients became worse after an adequate trial. Cessation of therapy was effected by progressive reduction in dosage over a three- to six-day period. Six patients received a course of nitrogen mustard therapy preceding the termination of a second course of cortisone in an attempt to determine if any additive effect could be observed.

A salt-poor diet was given if edema or hypertension was noted. Potassium chloride was administered in an attempt to influence muscle weakness when it occurred. Testosterone propionate was given to one patient in an attempt to promote wound healing by the production of positive nitrogen balance.

CASE REPORTS

CASE 1. A fifty-three year old white male was admitted on May 11, 1950, because of dyspnea. In October, 1947, he first noted the appearance of right cervical, inguinal and axillary nodes. The nodes had progressively enlarged and he received radiotherapy at another hospital. He was emaciated. There was orthopnea, tachypnea and dyspnea, pleural effusion in the lower two-thirds of the right chest, hep-

* Acknowledgment is made of the courtesy of Dr. C. G. Grand of New York University who performed the tissue culture studies.

atomegaly 12 cm. below the right costal margin in the mid-clavicular line, splenomegaly 3 cm. below the left costal margin in the anterior axillary line and 1 to 2 cm. palpable cervical nodes. X-ray of the chest revealed bilateral pleural effusion, massive on the right, and osteosclerosis of D11. Roentgen examination of the gastrointestinal tract revealed retrogastric nodal enlargement. Bone survey also revealed lytic and blastic lesions of both humeri. Red count on admission was 3,670,000, with 11.6 gm. hemoglobin. The white blood count was normal. Sedimentation rate was 28 mm./hr. A lymph node biopsy disclosed Hodgkin's sarcoma.

The patient required right thoracentesis with removal of 1 L. of fluid about once weekly. Up to June 15th his temperature reached 100 to 101°F. daily. On June 15th cortisone therapy, 100 mg. intramuscularly daily, was instituted and continued until June 29th. Initially the fever diminished but by June 26th it again reached 100°F. daily. Symptomatically there was very little response, the only procedure that seemed to benefit the patient being repeated thoracenteses. On July 3rd cortisone therapy was instituted in doses of 100 mg. intramuscularly three times weekly for eighteen days. No beneficial effects were noted, the patient continuing to get worse. From July 24th to August 13th cortisone was increased to 100 mg. daily and from August 14th to September 3rd the patient was afebrile. Otherwise there was no symptomatic improvement and nodes and hepatosplenomegaly were unchanged.

Beginning August 31st the patient was given nitrogen mustard, 0.1 mg./kg. of body weight intravenously, for four days. He had moderate nausea and vomiting following the first injection of nitrogen mustard and none with the subsequent three. On September 3rd he again became febrile, his temperature reaching 100°F. daily. He complained of hoarseness and severe throat pain. On September 4th an easily removable yellow-white, spotty exudate on the palate and pharynx showed alpha streptococci and nonpathogenic Neisseria. By September 5th the patient was completely aphonic. The white blood count fell after nitrogen mustard therapy to 1,000, with no change in the differential. Platelets which had been 70,000 prior to nitrogen mustard therapy fell progressively to 8,000 on September 11th. The patient was treated with penicillin intramuscularly and aureomycin mouth washes, with improvement in the exudate. However, laryngoscopy showed weakness of both cords and suggestion of a contact ulcer posteriorly. On September 11th purpuric spots were noted all over the body. Transfusion of fresh whole blood was ineffective and the patient expired on September 11th.

Eosinophil counts are recorded in Figure 8. Plasma potassium showed no definite change effected by cortisone, remaining high normal. Total body potassium values are given in Figure 9. Red blood count and hemoglobin remained at the transfused level obtained just prior to cortisone therapy during the first twenty days of treatment with cortisone. Thereafter there was a slight decrease to a level averaging 3,700,000 red blood cells and 13.4 gm. of hemoglobin. Plasma sodium dropped from 140.5 to 132.2 mEq. I^{131} uptake by the thyroid is charted in Figure 10. The patient developed marked pretibial edema while on cortisone but his serum albumin was 2.7 gm./100 cc. Blood pressure readings remained unchanged during therapy except for a short period from June 24th to June 30th when the systolic pressure ranged between 140 and 160 and the diastolic pressure was 90 to 100. Marrow prior to therapy was hypocellular with increased numbers of lymphocytes. On the seventh day of cortisone treatment there was a marked increase of reticulum cells, a shift to the right in the myelocytic series, a slight increase in eosinophils, a marked increase in erythroblasts and normoblasts, and an increased cellularity characterized by more abundant mitoses and many more clumps in the aspirate. On the fourteenth day of therapy there was a dramatic shift to the left in the myelocytic series, a decrease in lymphocytes and a further increase in cellularity due primarily to increased numbers of erythroblasts and normoblasts. At the same time increased numbers of megakaryocytes were noted which appeared to have engulfed red blood and white blood cells.

Marrow cellularity continued to increase during the next ten weeks of therapy progressively, with the increase being due to myelocytic proliferation. Many multinucleated reticulum cells were observed during the last eight weeks of therapy.

Autopsy disclosed Hodgkin's granuloma and sarcoma involving pleura, right lung, liver, esophagus, stomach, duodenum, para-aortic, paraesophageal and abdominal lymph nodes, femora, left scapula and vertebrae (D4 and D5). Of particular interest were a large ruptured

gastric ulcer measuring 2 cm. in diameter on the lesser curvature 5 cm. from the pylorus, and a perforating ulcer of the first portion of the duodenum on the posterior wall. Both showed Hodgkin's infiltration and little evidence of healing or serosal reaction. There were also guanazolo without any response.[21] His temperature reached 101° to 102°F. daily. He complained of generalized weakness, back pain, cough and loss of weight.

On June 15th therapy with cortisone was begun (Fig. 1) in doses of 100 mg. intramuscu-

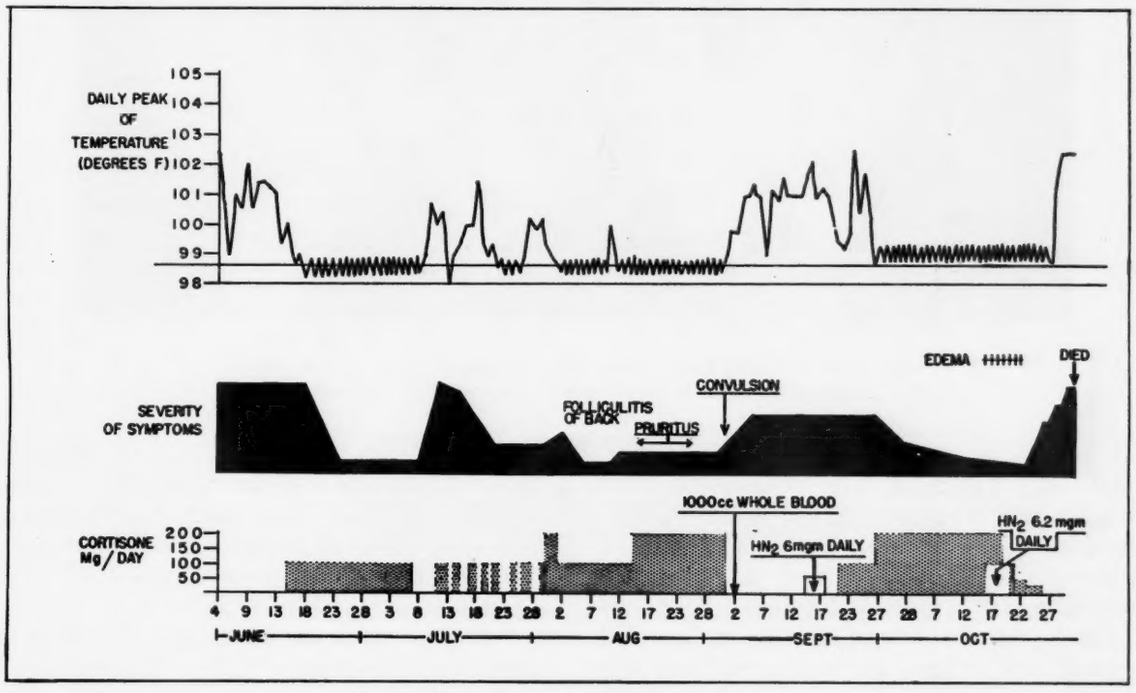

FIG. 1. Case II. Course with cortisone therapy.

small erosions of the esophagus, jejunum and ileum. The adrenal cortices showed evidence of atrophy and two small areas of Hodgkin's infiltration. No morphologic alterations in the Hodgkin's tumor cell were found which could be attributed to cortisone.

CASE II. A thirty-five year old white male was admitted on February 1, 1950, because of increasing fatigability, backache, pain in the right scapula and arm and numbness of the right fifth finger. The onset of symptoms of Hodgkin's disease was early in 1948. Since then the patient had had five courses of nitrogen mustard therapy and irradiation of cervical, mediastinal and retroperitoneal nodes. The diagnosis of Hodgkin's granuloma was confirmed here after biopsy of a supraclavicular node. Physical examination was essentially negative except for the presence of a 3 cm. right supraclavicular node and smaller left supraclavicular nodes. X-rays of the chest demonstrated nodal and parenchymal disease. The patient was treated for fourteen days with larly daily. On the day cortisone therapy was begun the patient's temperature returned to normal and he remained afebrile while on cortisone. Symptomatically there was considerable improvement during this period with brightening of affect, increase in appetite, increase in strength and lessening of cough. However, the nodes remained unchanged and x-rays of the chest showed no essential change. Three days after cortisone was stopped on July 6th fever recurred, reaching 101°F. daily with renewal of malaise, anorexia and weakness. On July 11th cortisone was reinstituted in dosage of 100 mg. three times weekly until August 1st. On this dosage the temperature remained elevated, reaching 100°F. daily. There was moderate improvement in symptoms but not to the extent noted during the initial course with 100 mg. daily. On August 1st the patient was placed on 200 mg. for two days followed with 100 mg. daily until August 13th. On this dosage he became afebrile and there was further improvement in symptoms. However, increasing

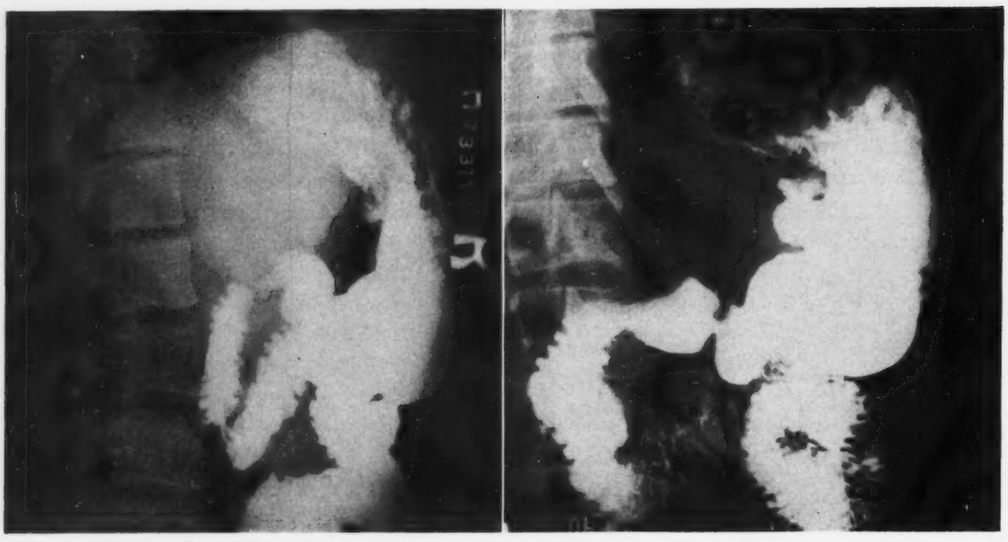

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FIG. 2. Case II. Large gastric ulcer before therapy.
FIG. 3. Case II. Increase in size of gastric ulcer during cortisone therapy.

dull, substernal aching developed. Folliculitis of the back appeared. The patient was then given 200 mg. of cortisone daily, which was continued until August 31st. With this dosage the patient remained afebrile and the moderate improvement in symptoms continued but pruritus developed. On August 31st the patient had a grand mal seizure. He recovered from this spontaneously and cortisone was discontinued. On September 1st fever recurred and thereafter reached 103°F. daily. The next day tarry stools were observed and vague symptoms of upper abdominal distress became more characteristic of peptic ulcer. The gastrointestinal series taken on June 28th had revealed the presence of several ulcers on the lesser curvature of the stomach in the pars media associated with some rigidity. (Fig. 2.) The tarry stools subsided in two days and the patient was transfused. Weakness, anorexia and fatigability were progressive from this point. On September 14th the patient was given nitrogen mustard, 0.1 mg./kg. of body weight intravenously daily, for four days. No improvement in symptoms was noted and the patient remained febrile. In spite of the convulsive episode cortisone, 100 mg. intramuscularly daily, was begun again on September 20th. This produced no apparent change and on September 27th the dose was increased to 200 mg. daily. By October 1st the patient was again afebrile and there was once again improvement in all symptoms. Gastrointestinal series on October 12th showed increase in size of the previously noted ulcers. (Fig. 3.) Nitrogen mustard was again given beginning October 16th. Cortisone, 200 mg. daily, was continued until completion of nitrogen mustard therapy on October 19th, then reduced gradually until it was stopped on October 26th.

Two days after discontinuance of cortisone fever recurred reaching 102°F., with recurrence of all symptoms and marked tachycardia. The patient expired on October 31st.

Eosinophil counts are recorded in Figure 8. Plasma potassium levels were not affected by cortisone therapy. Total body potassium showed a fall. (Fig. 9.) I^{131} uptake by the thyroid is charted in Figure 10.

Marrow prior to therapy was hypocellular with a slight increase of lymphocytes. On the seventh day of cortisone treatment there was an increase in reticulum cells, a moderate shift to the right in the myelocytic series, a decrease in lymphocytes, marked normoblastosis and increase in cellularity characterized by increased numbers of mitotic figures. On the fourteenth day of cortisone therapy there was a marked increase in eosinophils and persistent normoblastosis. On the twenty-first day of therapy increased normoblastosis was observed with greater cellularity. At this time an increase in megakaryocytes and multinucleated reticulum cells was noted. Some of the megakaryocytes were observed to contain inclusions which appeared to be engulfed red blood cells.

During the next two months of treatment

cellularity increased due to myelocytic series cell proliferation. Normoblastosis was no longer evident.

Autopsy revealed Hodgkin's sarcoma with marked anaplasia involving retroperitoneal, perirenal and mediastinal nodes, massive parenchymatous pulmonary involvement with cavity formation in the right upper lobe, gastric ulcerations and infiltration of liver, diaphragm, bone and right adrenal gland. Many eosinophils were noted in the involved areas. Two gastric ulcers were present along the lesser curvature in the area of the pars media, both of which showed microscopically extensive sarcomatous involvement of mucosa, submucosa and muscularis. The adrenal cortices were atrophied to one-third to one-fourth of normal and the right adrenal had several small areas of Hodgkin's infiltrate. No morphologic changes ascribable to cortisone were found.

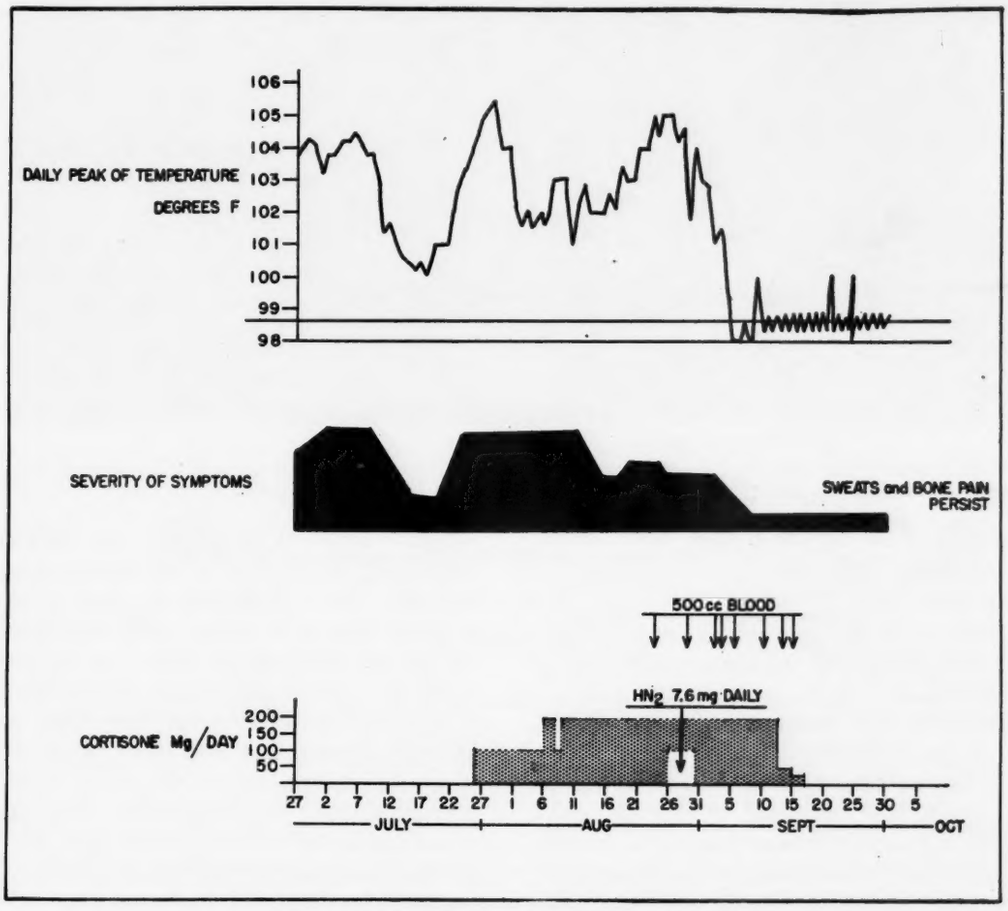
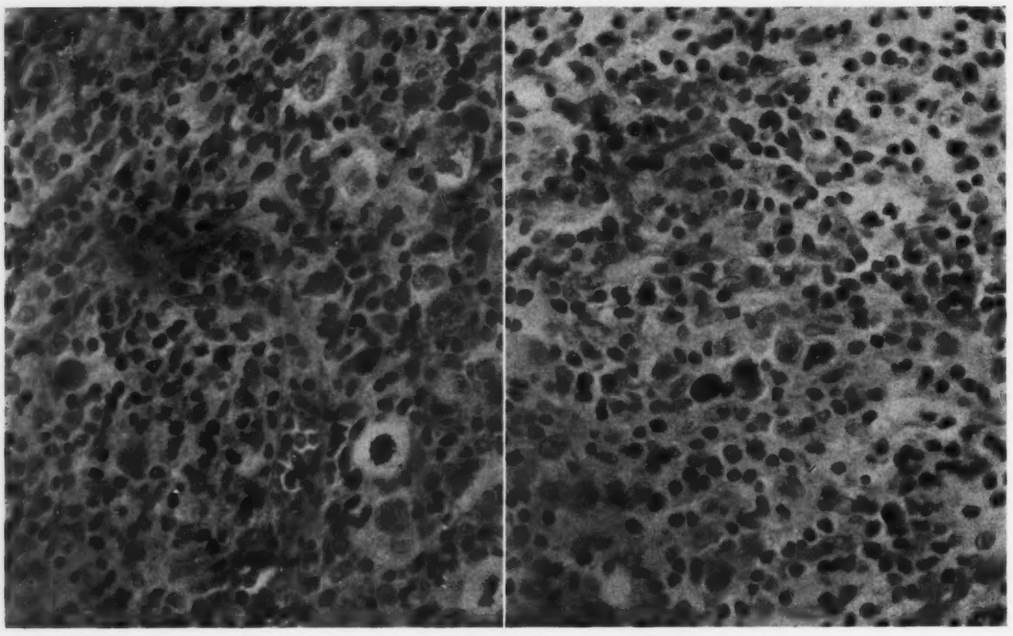


FIG. 4. Case III. Course with cortisone therapy.

CASE III. A thirty-three year old white male was admitted for the third time on June 26, 1950, complaining of fever, weakness and dizziness of ten days' duration. Diagnosis of Hodgkin's disease was first made elsewhere in 1947. Lymph node examination here revealed Hodgkin's granuloma. The response to repeated courses of nitrogen mustard therapy was transient.

Physical examination on admission showed no adenopathy. The liver edge was palpable at the costal margin; the spleen was palpable 2 cm. below the costal margin on deep inspiration. Red blood cell count on admission was 3,990,000, with 13.8 gm. of hemoglobin; white blood count was 1,700, with 59 per cent neutrophils of which 25 per cent were bands, 17 per cent lymphocytes, 22 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. Sedimentation rate was 29 mm. per hour. The patient's temperature ranged between 102° to 105°F. There were severe night sweats, fatigability, anorexia and weakness. X-rays of the chest showed no significant mediastinal adenopathy. Gastrointestinal series showed anterior



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FIGS. 5 and 6. Case IV. Sections of biopsies of Hodgkin's lymph nodes before and after six weeks of cortisone therapy. There is a marked diminution in the number of eosinophils in Figure 6.

displacement of the stomach. Red blood count and hemoglobin fell progressively so that by July 28th these were 2,860,000 and 9.2 gm. The white blood count was persistently low, usually below 1,500 cells, with no essential change in the differential.

Cortisone therapy was instituted on July 27, 1950, in doses of 100 mg. daily until August 6th. (Fig. 4.) Since there was no symptomatic response, dosage was increased to 200 mg. daily on August 8th and continued until September 12th when dosage was gradually decreased until the hormone was discontinued on September 16th. With increase in cortisone dosage there was an improvement in muscle weakness and in affect, with mild euphoria for about one week. Mooning of the face was observed. The fever was unchanged, the anemia and leukopenia persisted and the sedimentation rate remained elevated. Fasting eosinophil counts were extremely low before therapy and were unchanged by cortisone. Plasma potassium was normal before and during therapy. Total body potassium was unchanged by cortisone therapy. Plasma sodium was normal until August 23rd when it dropped to 124.6 mEq. There was no definite change in CO_2 combining power or chlorides. I^{131} uptake by the thyroid is charted in Figure 10.

The patient was given nitrogen mustard intravenously in doses of 0.1 mg./kg. for four days beginning August 29th. He was continued on cortisone for approximately two weeks after nitrogen mustard therapy. During this period the white blood count fell progressively until it reached 250 on September 5th at which level it hovered for another ten days. He was given multiple transfusions and after September 16th there was a progressive rise in the count until it reached 3,200 on September 25th. With the transfusions the red blood count and hemoglobin also reached normal levels and on September 18th the red blood count was 5,300,000 and hemoglobin 17.4 gm. The sedimentation rate was 14 mm./hr.

Immediately after administration of nitrogen mustard there was a fall in the temperature to normal levels, there was marked improvement in all symptoms and the spleen could no longer be felt. This remission has persisted to the present, two and a half months after completion of nitrogen mustard therapy.

The bone marrow prior to treatment was hypocellular. It contained increased numbers of lymphocytes and, from the appearance of the smeared particles, a large amount of fibrous tissue. On the eighth day of cortisone therapy there were essentially no changes in the marrow findings. On the nineteenth day of treatment there was a marked increase in the cellularity

of the marrow evidenced by increased numbers of particles in the aspirate fluid and an increased number of mitotic figures. At this time there was a marked increase in reticulum cells, an increase in immature eosinophils, a great increase in mature eosinophils, a marked decrease in lymphocytes, an erythroblastosis and normoblastosis and an increase of megakaryocytes associated with large multinucleated cells. At this time the marrow was no longer fibrotic. On the twenty-sixth day of treatment the changes continued with the exception of decreased numbers of mature eosinophils and a more marked erythroblastosis.

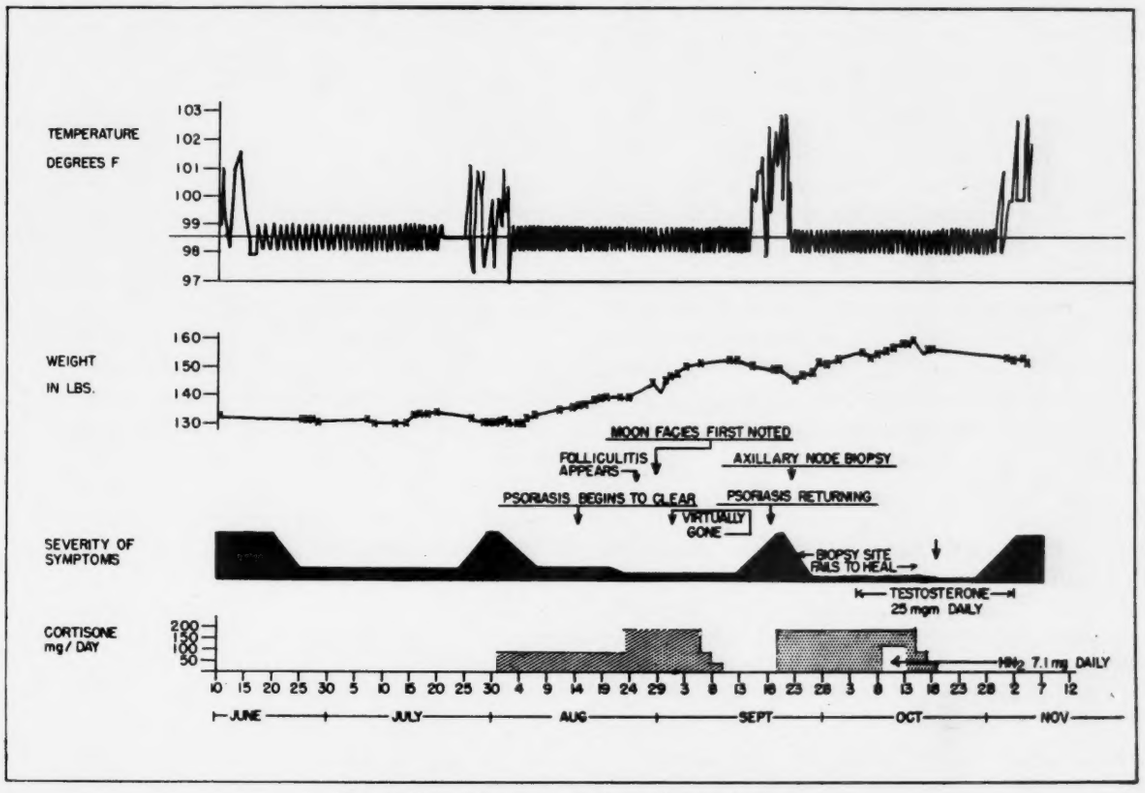

FIG. 7. Case IV. Course with cortisone therapy.

CASE IV. A thirty year old white male was admitted June 10, 1950, because of malaise and weight loss. Hodgkin's disease was diagnosed elsewhere and he was given nitrogen mustard therapy in March, 1950, with transient benefit. Pertinent findings were the presence of axillary and cervical lymphadenopathy and widespread psoriatic skin lesions. His red blood count was 4,400,000 with 12.9 gm. of hemoglobin, sedimentation rate 25 mm./hr., white blood count 18,200 with 92 per cent neutrophils (20 per cent bands), three lymphocytes, four monocytes and one basophil. On June 29th another cervical lymph node biopsy was performed. Microscopically this node showed both Hodgkin's paragranuloma and granuloma with the former involving the greater part of the node. (Fig. 5.)

During the last week of July the patient became febrile, his temperature reaching 101°F. daily. Anorexia and weight loss appeared. The tip of the spleen became palpable. He complained of pain in the left sacroiliac region. Bone survey was negative. He was placed on a salt-poor diet and given cortisone, receiving 100 mg. daily from July 31st to August 22nd and then 200 mg. daily until September 5th. (Fig. 7.) At this time cortisone was progressively reduced until discontinuance on September 10th. On July 30, 1950, the white blood count was 15,900, red blood count was 4,570,000 with 14.6 gm. hemoglobin and the sedimentation rate was 23 mm. per hour. Promptly after starting cortisone the patient became afebrile, the severe back pain disappeared in twenty-four hours, his appetite improved and he had a general sense of well-being. There was no change in size of palpable lymph nodes but at the end of therapy the tip of the spleen was no longer palpable.

Psoriatic lesions showed considerable improvement after four weeks' treatment. The peripheral white blood count fell to 9,000 to 12,000, with the shift to the left persisting. On September 12th the sedimentation rate was 5 mm. per hour. There was also a steady rise in red blood count and hemoglobin in this period to 5,500,000 cells and 18.1 gm. hemoglobin on September 12th. By September 5th his weight had risen to 151 pounds from an initial weight of 131 pounds, with only slight evidence of edema. Rounding of the face was present. Blood pressure was essentially unchanged. Blood sodium showed no change after four weeks of therapy. Blood volume was 4.45 L. with hematocrit of 38 prior to treatment. After three weeks of therapy blood volume was 4.88 L. with hematocrit of 45.3. Twenty-four-hour I^{131} uptake is noted in Figure 10. There was no change in plasma potassium, CO_2 combining power or chlorides during therapy. Eosinophil counts are given in Figure 8.

The patient maintained this general improvement for three days after discontinuance of cortisone. On September 14th weakness recurred and the sense of well-being diminished. The patient became febrile once more on September 14th and temperature began to range between 100° and 103°F. Loss of appetite and loss of weight developed. Psoriatic lesions reappeared on September 18th. New lymph nodes became palpable in the cervical and axillary regions and the patient complained of paresthesias. On September 20th cortisone therapy was begun again in dosage of 200 mg. daily until October 14th, with gradual reduction in dosage until it was discontinued on October 19th.

On September 22nd another lymph node biopsy was performed, again showing Hodgkin's granuloma. (Fig. 6.) However, there was a marked diminution in the number of eosinophils as compared with the previous biopsy. Two days after resumption of cortisone therapy the patient became afebrile. Appetite returned with an improved state of well-being. On October 3rd the white blood count was 16,550 with shift to the left and the red blood count was 5,100,000 with 16.8 gm. hemoglobin. Leukocytosis persisted until October 17th when it fell to 6,500 with a shift to the left. The sedimentation rate fell to 12 mm. per hour.

The biopsy site did not heal while under cortisone. Lymph oozed in fair quantity on pressure. The patient was placed on testosterone propionate, 25 mg. intramuscularly daily, on October 5, 1950, until November 2nd. This apparently produced no effect on wound healing. With continuance of cortisone palpable nodes again diminished in size, weight gain again became evident and the patient was given a course of nitrogen mustard therapy to see if improvement could be maintained for a considerable period. There were no toxic symptoms as a result of nitrogen mustard.

After discontinuance of both cortisone and nitrogen mustard wound healing became evident. The patient remained symptom-free for approximately two weeks until October 31st when there was enlargement of left cervical lymph nodes, decrease in appetite and temperature elevation to 101°F. The spleen again became palpable. X-ray of chest showed right paratracheal and left hilar nodal enlargement. Gastrointestinal series on November 8th demonstrated the presence of a mass displacing the duodenal bulb and descending duodenum anteriorly. The sedimentation rate rose to 22 mm. per hour on November 1st. At this point it was decided to treat the patient with irradiation. The fever and lymphadenopathy diminished following roentgen therapy.

Case v. A twenty-six year old white male was admitted for the fourth time for the treatment of Hodgkin's disease on June 5th, 1950. The onset of the disease was in September, 1947, with persistent cough, easy fatigability and fever. Left cervical lymph node biopsies in February, 1948, and October, 1948, established the diagnosis of Hodgkin's paragranuloma showing transition to granuloma. Chest x-ray demonstrated a large dense mass in the left upper lung field. The patient was treated with irradiation to the chest in April and May of 1948. In December of that year there was a recurrence of the left pulmonary lesion with hilar adenopathy and the generalized symptoms reappeared. The patient again received radiotherapy. From the time of onset of the disease the patient was never completely in remission, his symptoms varying in intensity but never absent.

His complaints on readmission on June 5, 1950, were marked fatigability, weakness, dyspnea on the slightest exertion, anorexia, weight loss and pain in the sacral area. Positive findings were emaciation, tachypnea, tachycardia, small, hard, posterior right cervical nodes and a large mass in the right posterior auricular region. X-ray of the chest revealed areas of infiltration in both mid-lung fields as well as increase in

extent of hilar densities bilaterally. There was widening of the superior mediastinum and a pleural reaction over the left upper lung field. There was widespread bone involvement. During the first two weeks in the hospital the patient's temperature varied between 99° and 100°F. His red blood count in this period varied between 3,700,000 and 3,940,000. The hemoglobin was between 11.6 and 12.7 gm. and the sedimentation rate between 23 and 27 mm. per hour. The white blood count was between 11,700 and 28,100, with a marked shift to the left.

On June 15th the patient was placed on cortisone, 100 mg. intramuscularly daily, until July 5th. There was improvement in appetite, muscle strength and general appearance. The fever was unaffected and adenopathy was unchanged. The patient was then placed on cortisone, 100 mg. intramuscularly, three times weekly until July 24th. During this period there was an increase in symptoms with increase in muscle weakness, diminution in appetite and increase of pains in the thigh region. On July 24th the patient was again placed on 100 mg. of cortisone daily until August 13th. The red blood count and hemoglobin increased without transfusions to a level between 4,600,000 and 4,750,000 red blood cells and 14.6 to 15.4 gm. hemoglobin. Sedimentation rates and white blood counts and differentials remained unchanged. On 100 mg. of cortisone daily there was again a general improvement in symptoms but not to the level achieved during the first course with equivalent dosage. On August 14th cortisone was increased to 200 mg. daily and kept at this level until August 31st. On this dosage there was no change in the febrile course or in size of nodes. The general sense of well-being was maintained but the patient complained of weakness of both legs. The increase in red blood cell count and hemoglobin was maintained but the sedimentation rate, white blood count and differential were unchanged.

Nitrogen mustard, 0.1 mg./kg. of body weight intravenously, was given for four days beginning August 29th. There was no toxic reaction. There was the usual fall in white blood count following nitrogen mustard to as low as 5,400, with no change in the differential count. Sedimentation rate fell to 14 to 16 mm./hr. and remained at that level until September 28th. However, the fever was unchanged and symptomatically there was no improvement. By the third week in September the patient complained of marked dyspnea, muscle weakness and loss of appetite. By September 14th there was a fall in red blood count and hemoglobin which went as low as 3,800,000 and 12.6 gm. on September 19th although the sedimentation rate remained at 14 to 16 mm./hr.

On September 19th cortisone in doses of 200 mg. daily was reinstituted and continued until October 13th when dosage was gradually reduced until cortisone was stopped on October 19th. Once again there was improvement in appetite, muscle strength, dyspnea and well-being. For the first time, on September 26th, diminution of the large right posterior auricular mass was noted which continued to recede until it was virtually unnoticeable. It is to be noted that nitrogen mustard therapy had been concluded on September 1st. During this period red blood count and hemoglobin again rose to about normal level, initial leukocytosis reappeared and sedimentation rate rose to 21 to 22 mm./hr. The patient's temperature began to reach levels of 102°F. by October 9th. On October 10th he again began to complain of increasing muscle weakness. A second course of nitrogen mustard was begun on October 10th. There was one episode of transient nausea. The fever, however, persisted with temperature reaching 103°F. on October 19th. There was essentially no response to the nitrogen mustard.

By October 23rd there was a marked increase in dyspnea, tachypnea and orthopnea. The heart rate, which had always been about 120 per minute, increased to 160 to 172 per minute. The electrocardiogram revealed a regular sinus rhythm. Digitalization and parenteral mercurial diuretics were ineffective. On October 22nd cortisone, 200 mg. intramuscularly daily, was reinstituted and continued until October 30th. Weakness became very marked and potassium chloride, 5 gm. daily in divided doses, was given. The patient's condition continued to deteriorate; he became cyanotic and was placed in an oxygen tent. There was no change in respiratory symptoms and the patient expired on November 1st. Permission for autopsy was not granted.

Prior to institution of cortisone therapy fasting eosionphil counts and the response to epinephrine were normal. There was no definite change during cortisone therapy. Total body potassium is given in Figure 9. Plasma potassium was normal until August 23rd when it dropped to 3.7 mEq. X-rays of the chest and bone surveys did not show any essential change during the

patient's course. A liver biopsy performed terminally showed miliary tuberculosis. CO_2 combining power was fairly high prior to and during cortisone therapy and bore no relationship to therapy. I^{131} uptake is charted in Figure 10. Plasma sodium was unchanged during therapy as was the blood pressure. Rounding of the face and edema developed to varying degrees during the course as did acneiform skin lesions.

The bone marrow prior to therapy was not remarkable except for increased numbers of lymphocytes. On the seventh day of cortisone treatment there was a slight increase of reticulum cells, a slight shift to the left in the myelocytic series, a marked increase of erythroblasts and normoblasts, an increase in marrow cellularity and an increase in the number of mitotic figures. Megakaryocytes appeared vacuolated and some appeared fat-laden. There was a decrease in lymphocytes. On the fourteenth day of therapy there was an increase in immature and mature eosinophils and a more marked normoblastosis. During the next ten weeks of treatment the marrow became progressively more cellular due to myelocytic series cell proliferation. Occasional multinucleated reticulum cells were observed.

Case VI. This patient was a forty-eight year old white male. After three weeks of fever, cervical lymphadenopathy, hepatosplenomegaly and weight loss in February, 1950, he was hospitalized elsewhere where a lymph node biopsy was performed. A diagnosis of Hodgkin's disease was made and the patient was transferred here on March 31, 1950. There was generalized lymphadenopathy, moderate hepatosplenomegaly and slight icterus. Pathologic diagnosis of another lymph node biopsy was Hodgkin's granuloma. The patient was febrile and anemic. The sedimentation rate was 37 mm. per hour. He was transfused and given terramycin, 3 gm. daily in divided doses, for seventeen days without response. Nitrogen mustard, 0.1 mg./kg. of body weight intravenously, was then administered for four days. Response was satisfactory and the patient was discharged on June 4, 1950.

After a symptom-free period of three weeks fatigability, anorexia and weight loss were noted and the patient re-entered this hospital July 26, 1950. On this admission he again had generalized lymphadenopathy, the liver edge was at the level of the umbilicus and the lower pole of the spleen was 8 cm. below the left costal margin. Superior mediastinal adenopathy and enlarged retrogastric nodes were noted. The red blood cell count was 2,250,000, with a hemoglobin of 7.6 gm. Sedimentation rate was 36 mm. per hour. The white blood count was 2,400, with 79 per cent neutrophils, 10 per cent lymphocytes, 9 per cent monocytes and 2 per cent eosinophils. Serum bilirubin was 5.2, alkaline phosphatase 16.6 units and cephalin flocculation 3 plus. Serum albumin was 3.7 gm. per cent, serum globulin 2.4 gm. per cent and blood urea nitrogen 56 mg. per cent.

After several transfusions cortisone therapy was begun on August 10, 1950. Two hundred milligrams daily were given for two days and then 100 mg. daily until August 22nd. From that time to September 2nd 200 mg. of cortisone were given daily. On August 14th symptomatic improvement was noted. There was considerable improvement in appetite and increase in strength. Euphoria was noted. On August 16th questionable diminution in size of peripheral nodes and hepatosplenomegaly was noted. By August 20th anorexia had recurred and the sense of well-being was gone. The patient was afebrile between August 11th and 15th but from then on his temperature ranged between 100° and 103°F. From August 19th on there was again increasing weakness. Blood urea nitrogen on August 28th was 36 mg. per cent but had risen to 75 on September 1st. Throughout his course his total white count remained low with a shift to the left, with neutrophils as high as 96 per cent.

In spite of repeated transfusions red blood cell count and hemoglobin remained at the initial low levels. There was no essential change in chlorides or CO_2 combining power during the course. Total body potassium, which was 2,570 mEq. prior to therapy, fell to 1,950 mEq. on August 29th. The blood pressure and plasma sodium remained unchanged throughout therapy. The patient was placed on a low salt diet on August 21st. On the 25th moderate pedal edema was noted and persisted throughout the remaining course. The serum bilirubin remained elevated, with a marked increase in jaundice noted on August 27th. On the 30th nitrogen mustard, 0.1 mg./kg., was given intravenously for four days. Cortisone was discontinued on September 3rd. On September 5th the patient expired. Permission for autopsy was not granted.

Marrow prior to treatment was hypocellular and contained an increased number of lymphocytes. On the seventh day of cortisone therapy

the marrow was more cellular as evidenced by increased numbers of particles in the aspirate fluid and by increased numbers of mitotic figures. At this time there was an increase in reticulum cells, a shift to the left in the granulocytic series, a twofold increase in immature eosinophils and a sevenfold increase in mature eosinophils, an increase in plasma cells, an increase in megakaryocytes which appeared to have engulfed red blood cells, a decrease in lymphocytes and marked normoblastosis. On the fifteenth day of treatment these changes were more marked with the exception that the numbers of mature and immature eosinophils had decreased and that there was marked erythroblastosis.

CASE VII. A twenty-seven year old white male was admitted on August 14, 1950, because of herpes zoster of the right shoulder, axilla and chest. A diagnosis of Hodgkin's sarcoma based on a lymph node biopsy had been made here in January, 1949. Treatment had consisted of several courses of radiotherapy to cervical, axillary and mediastinal nodes.

After healing of the herpes the patient had a low grade fever ranging between 99° and 100°F. His red blood count ranged between 3,750,000 and 3,920,000. The hemoglobin was 12.4 to 12.9 gm. and the sedimentation rate 19 to 26 mm. per hour. There was moderate right anterior cervical and left supraclavicular adenopathy. X-rays of the chest showed no essential change in comparison with those at the time of his last discharge from the hospital. The patient had moderate to marked fatigability and some diminution in appetite.

Cortisone therapy was begun September 13, 1950, with 200 mg. daily until October 20th when the dosage was gradually reduced until cessation of therapy on October 26th. With cortisone there was a marked increase in appetite. Distinct euphoria developed after three weeks. "Moon facies" was observed at the same time. Acneiform lesions were noted in four weeks. The low grade fever persisted and there was no essential change in the lymphadenopathy. There was an increase in blood pressure from 130/90 to 160/110 in the last three weeks of therapy. After discontinuance of cortisone blood pressure levels returned to normal. There was no edema. Twenty-four hour uptake of I^{131} is noted in Figure 10. Sedimentation rate remained between 19 to 22 mm. per hour. There was a rise in red blood count and hemoglobin to an average of 4,600,000, with 15.0 gm. of hemoglobin after one month of treatment. The white blood count was persistently over 10,000 with no change in the differential after cortisone therapy was instituted.

On October 16th nitrogen mustard, 0.1 mg./kg., was given intravenously for four days. There was definite regression in size of all nodes which began promptly on the fourth day of mustard therapy. There was nausea and vomiting after the first dose but none thereafter. The patient was well after nitrogen mustard therapy until November 9th when his temperature began to rise to 101°F. This elevation persisted until November 20th. Accompanying it was tachycardia and tremor of the hands. Gastrointestinal symptoms prompted x-ray studies which demonstrated retrogastric nodal involvement on November 28th. Three months previously they were negative. The patient was given radiotherapy to the abdominal nodes.

CASE VIII. A thirty-five year old white male was readmitted June 7, 1950, because of recurrence of adenopathy, fever and anorexia. In December, 1947, he first noted a lump in the left axilla which was biopsied and a diagnosis of Hodgkin's granuloma made. Since then he had been treated with radiotherapy and nitrogen mustard. In February, 1950, x-ray examination showed bilateral hilar and paratracheal adenopathy, retrogastric and retroduodenal adenopathy and osteoblastic involvement of the eleventh and twelfth dorsal and first and second lumbar vertebrae. He again received a course of nitrogen mustard therapy February 20th to the 23rd in the usual dosage. In March a course of x-ray therapy to the entire paraspinal region was initiated and continued until May 12th. It was then discontinued because of leukopenia. At that time he was asymptomatic and was discharged.

Symptoms recurred within one week of discharge and the patient was readmitted on June 7th. He was febrile, anemic and had generalized lymphadenopathy. The liver was palpated 4 cm. below the right costal margin in the midclavicular line and the spleen was palpable 3 cm. below the left costal margin in the midclavicular line.

On June 15th the patient complained of dysphagia which steadily increased until only liquids were tolerated after June 22nd. On June 20th he also began to complain of hoarseness which was progressive.

Cortisone therapy was instituted on June 22nd. He received 300 mg. intramuscularly in divided doses on the first day and then 100 mg. intramuscularly daily. Because of progressive hoarseness the patient was laryngoscoped but the only finding was restriction of left cord movements. There was no response to cortisone therapy. There was no improvement in affect, the course being distinguished by depression and fits of weeping. The patient's temperature was unchanged, nodal adenopathy unaffected and one week after beginning cortisone the liver was palpated 13 cm. below the right costal margin while the spleen remained unchanged. The patient's course was rapidly downhill and he expired on July 6th, thirteen days after the onset of cortisone therapy. Laboratory findings were significant only with regard to an eosinophilia up to 14 per cent. The total cosinophil count was 1,600 per cu. mm. and did not fall during treatment with cortisone.

The marrow revealed pronounced eosinophilia primarily of immature forms. There was no change after seven days of cortisone treatment. Autopsy disclosed Hodgkin's granuloma involving lymph nodes, liver, spleen, esophagus, bone, posterior pituitary and dura. The adrenals showed evidence of mild atrophy.

CASE IX. A forty year old Negro male was admitted on August 14, 1950. He complained of severe cough productive of one cupful of sputum, occasionally blood streaked, fever and weight loss of two weeks' duration. Physical examination revealed an acutely ill patient with diminished breath sounds and rales over both bases posteriorly, a firm liver palpable four fingerbreadths below the right costal margin, bilaterally enlarged axillary and inguinal nodes and a generalized papular eruption over the trunk and extremities. X-ray of the chest was normal. The red blood count on admission was 4,560,000, hemoglobin 14.5 gm., white blood count 2,000 with 48 per cent neutrophils, 51 per cent lymphocytes and one basophil. Sedimentation rate was 10 mm. per hour. The bromsulfalein test disclosed 11 per cent retention, alkaline phosphatase was 19.8 Shinowara units, albumin 3.5 gm. per cent, and globulin 3.2 gm. per cent. Biopsy of an axillary node and of the liver revealed Hodgkin's granuloma. The patient's temperature rose as high as 104°F. daily and the patient became steadily worse. The red blood count and hemoglobin fell to 2,990,000 and 9.4 gm., respectively, on September 20th, with platelets 6,500. On October 9th one dose of nitrogen mustard, 0.1 mg./kg. of body weight intravenously, was administered. The white blood count fell to 1,050 on the following day and to 750 on the day after. Nitrogen mustard was discontinued.

The spleen was now palpable four fingerbreadths below the left costal margin. On October 24th therapy with cortisone, 200 mg. intramuscularly daily, was begun. On the third day of treatment the patient's temperature fell to normal and his appetite improved. However, dyspnea was unchanged and an x-ray of the chest revealed bilateral basal densities not present on previous examinations. The afebrile course continued for only four days and thereafter the temperature gradually rose so that twelve days after instituting cortisone therapy it reached 102°F. daily. There was no improvement in leukopenia. Anemia persisted and the patient was transfused several times. He gradually became weaker and more dyspneic. Hepatosplenomegaly and palpable lymph nodes remained essentially unchanged. On November 17th, twenty-four days after instituting cortisone therapy, the patient expired. Autopsy permission was not granted.

Bone marrow examination before therapy revealed it to be more cellular than normal. There was erythroblastosis and normoblastosis with many mature and immature megakaryocytes. Rare tissue mast cells were observed. Bone marrow studies on the eighth and seventeenth days of treatment disclosed only a slight increase in normoblastosis.

CASE X. A forty year old white male was admitted on August 28, 1950, because of fever of two months' duration and a mass in the right axilla of twenty years' duration. He had first noted a small mass in the axilla in 1930 which had gradually increased in size until it was as large as an orange at the time of his induction into the Army in 1942. At that time it was lanced and did not reappear again for one or two years. It was then as small as a grape but gradually grew larger. In June, 1950, he noted the onset of fever with temperature ranging between 99° and 102°F.; and although his appetite was unchanged, there was progressive weight loss of 19 pounds. Physical findings included the presence of a spheric mass in the right axilla about 6 cm. in diameter, freely movable, soft and not tender, a liver palpable 3 cm. below the right costal margin in the mid-

clavicular line, and a palpable spleen tip. The red blood count on admission was 3,900,000, with 12.8 gm. hemoglobin. The white blood count was 1,300, with a differential count of 56 per cent neutrophils, 35 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophils and 1 per cent basophil. The gastrointestinal series revealed the presence of enlarged retroperitoneal nodes.

The patient's fever reached as high as 103°F. daily. An eosinophilia of 13 per cent was noted on September 7th. The highest white blood count was 2,000. Biopsy of the mass in the right axilla was performed on September 12, 1950. Diagnosis on microscopic examination was malignant lymphoma, possibly Hodgkin's disease. The patient was transfused several times. In spite of the persistent peripheral leukopenia nitrogen mustard therapy, 0.1 mg./kg. intravenously daily for four days, was instituted October 2nd. On October 8th the patient became afebrile until October 25th. On October 11th the white blood count was 750 with a marked shift to the left. The patient was transfused and maintained on antibiotic therapy. Otherwise he was symptomatically improved. This was short-lived and by October 28th he again began having daily fever as high as 103°F. with associated symptoms. During the period after nitrogen mustard therapy there had been no change in the hepatosplenomegaly nor in the residual of the right axillary mass.

Another sternal marrow aspiration on November 2, 1950, showed it to be much less cellular than on the original aspirate with a definite depression of the myeloid elements. Peripheral white count was again within the same range as on admission, namely, 1,000 to 1,500 cells.

On November 18th cortisone therapy was begun, 300 mg. intramuscularly in divided doses on the first day followed with 200 mg. daily thereafter. The response of the fever was immediate. The temperature did not rise above 99°F. after the second day of therapy. The patient felt symptomatically improved. Moon facies, ascites and ankle edema were noted on November 26th and the patient was placed on a low salt diet. Hepatosplenomegaly and the residual of the right axillary mass were unchanged. Blood pressure remained within normal limits. The white blood count was essentially unchanged. On December 14th another course of nitrogen mustard therapy was instituted following which cortisone therapy was reduced until it was discontinued on December 20th.

The bone marrow before therapy was hypocellular. There was a mature cell eosinophilia, the lymphocytes were increased and there were numerous reticulum cells, many of which were multinucleated. On the eighth day of treatment the marrow appeared less cellular than before treatment, as shown by few particles in repeated aspirates. However, by the twenty-first day of therapy the marrow was normally cellular due largely to normoblastosis and erythroblastosis. The lymphocytes decreased to normal levels and the eosinophils also decreased although not to normal. There was no essential change on the thirty-first day of treatment.*

RESULTS

There was distinct but transient subjective improvement in seven of the ten patients. This was manifested by a feeling of well-being, increase in strength and improvement in appetite. Three patients died within one month of the institution of therapy; one of these had shown a transient symptomatic response to cortisone. Six patients died during the study. Three of these were autopsied.

All ten patients were febrile at the time of institution of treatment. In three the temperature fell to normal while under therapy and rose with discontinuance of the hormone. In three there was a transient fall for a few days. In four there was no change. The effect on the size of involved organs or nodes was minimal. One patient had regression in the size of axillary and cervical nodes. Another patient had considerable regression in the size of a postauricular mass. However, this occurred twenty-five days after completion of nitrogen mustard therapy and may have been related to it.

There was weight gain in most of the patients. This was attributable at least in part to water retention. One patient gained 30 pounds with only minimal evidence of edema.

Three patients who showed some initial response became refractory to the effects of cortisone even with respect to subjective improvement after three weeks to three months of therapy.

Nitrogen mustard was effective in producing subjective and objective improvement in only

* Since submission of this paper for publication this patient has died. Autopsy on September 5, 1951, disclosed Hodgkin's granuloma.

one patient in whom cortisone failed or who became refractory to cortisone. No additive effect of cortisone and nitrogen mustard was observed.

LABORATORY DATA

The striking decrease in the number of circulating eosinophils following the administration

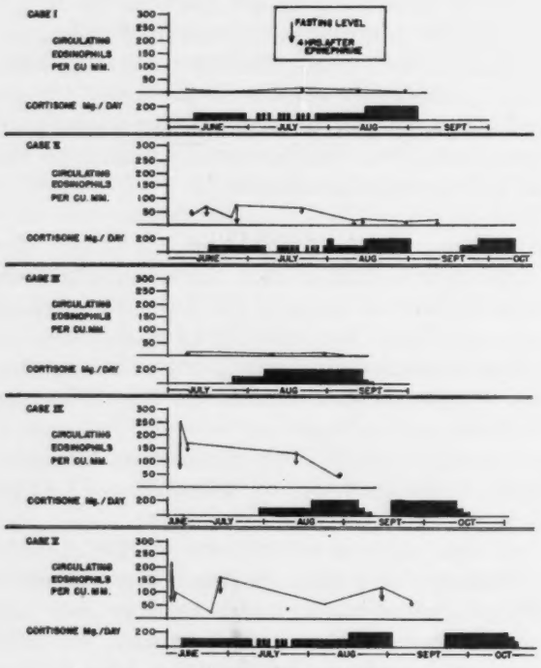

FIG. 8. Circulating eosinophil response.

of ACTH and their virtual disappearance from the blood after repeated doses is well known. Although there seems to be a common impression that the same phenomenon accompanies cortisone administration, Thorn[22] has stated that the effect is not nearly so striking as with ACTH; and Sprague et al.[23] failed to note any consistent eosinopenia resulting from cortisone therapy. Conn[24] noted a lag of forty-eight to seventy-two hours after cortisone administration before eosinopenia was manifested. Perera et al.[25] noted on regimens of 80 mg. of cortisone a day significant falls in the eosinophil counts in all three patients in whom they were followed.

The fasting level of circulating eosinophils and the response to epinephrine at various stages of therapy in the patients in this study are shown in Figure 8. The effect of cortisone is questionable. Although two patients showed a slight tendency to lower fasting counts during therapy, there was no definite change in the level of circulating eosinophils in three patients. It may be noted that in five of six patients with other diseases treated with cortisone (not included here) we have likewise failed to find marked eosinopenia even after weeks of therapy.

In one patient (Case VIII) not shown in Figure 8 there was marked eosinophilia with counts of 1,600 per cu. mm. before therapy and this was

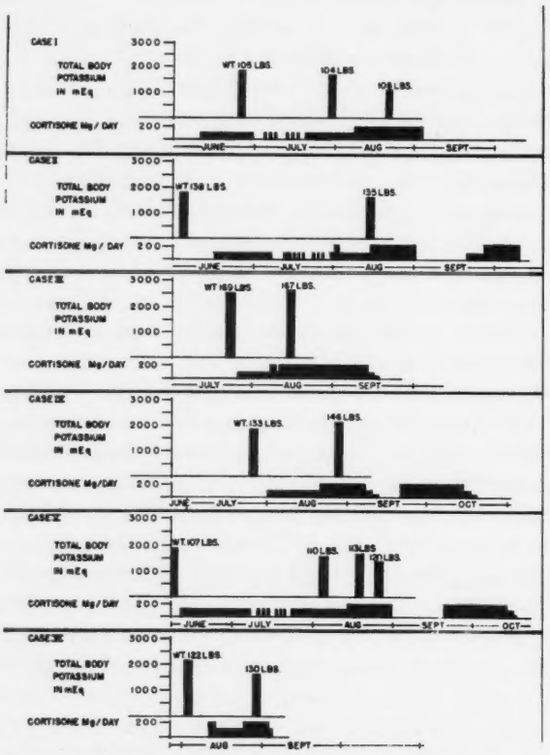

FIG. 9. Effect of cortisone on total body potassium.

not affected in the least by cortisone therapy in doses of 100 mg. a day as determined on the fifth and sixth days of treatment.

In spite of the known depressant effect of cortisone on the pituitary-adrenal-cortical system these patients failed to lose the eosinopenic response to epinephrine if it was present before therapy was begun.

It is interesting to note that three of the six patients adequately studied with regard to the eosinophil counts had very low levels before treatment was begun. This suggests that the adrenal cortex was reacting strongly to the stress of the disease, at least with respect to the eosinophil response. One of these patients also revealed a high level of urinary 17-ketosteroid excretion before treatment.

The blood volume and hematocrit were followed serially in five cases. In one patient the

blood volume gradually increased, finally doubling its pretreatment value after three and a half months of therapy. However, the initial volume was only 50 per cent of normal and so an abnormal elevation was not encountered. Furthermore the hematocrit remained unchanged throughout therapy so that the original plasma/red cell mass ratio remained constant. One patient manifested a moderate drop in total blood volume but this was proportional to a fall in hematocrit consequent upon the further development of progressive anemia. In the other three patients there were no significant changes in blood volume even though one showed marked edema and another slight edema.

The effect of cortisone on the total body potassium is shown in Figure 9. Four of the six patients studied showed moderate to marked decreases in the total body potassium although only one of these showed even a slight fall in the plasma potassium level (to 3.7 mEq. per liter). These results serve to illustrate directly the marked changes which may occur in the intracellular potassium content without reflection of abnormality in the plasma.

Six patients had repeated determinations of the plasma sodium concentration. There was no change in four patients and a slight fall was noted in two (Cases I and III). In one of these (Case I) marked dependent edema associated with hypoproteinemia had developed. In this patient, too, there was a slight drop in the serum chloride concentration toward the end of therapy. Both of these changes could, at least in part, be attributed to a low salt diet instituted in an effort to relieve the edema. None of the other patients showed any change in serum chloride concentration and there was no change in the level of serum CO_2 in any of the seven patients studied.

A decrease in the "accumulation gradient"[26] of radioiodine by the thyroid gland has been found in toxic goiter treated with ACTH.[27] However, the total radioiodine uptake at the end of twenty-four hours has been reported as unaffected.[28] Of the six patients in this group in whom serial tracer studies were performed only one failed to manifest a definitely diminished ability to concentrate the isotope in the thyroid. (Fig. 10.) In two of the patients following several weeks of cortisone therapy (Cases II and III) the twenty-four-hour readings were within the hypothyroid range during cortisone therapy. In only one patient (Case VII) included in this study was it possible to obtain a tracer determination following discontinuance of cortisone treatment. Within a week following withdrawal of the hormone thyroid activity had again increased.

In one patient (Case VII) there was no change

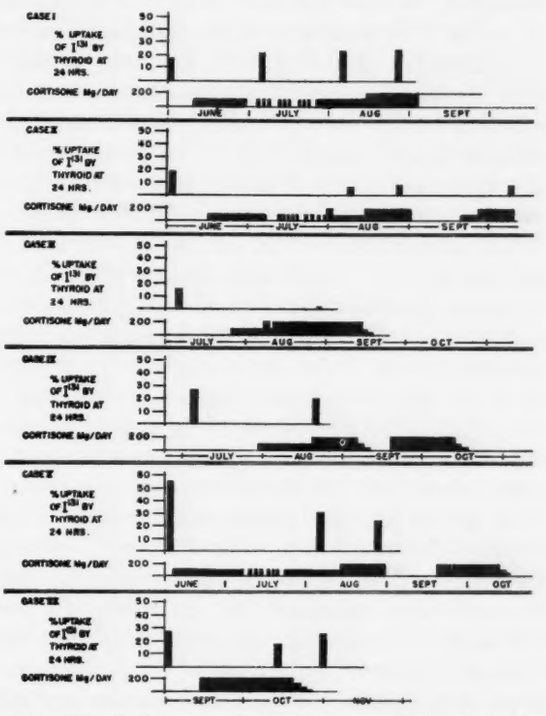

FIG. 10. Influence of cortisone on I^{131} uptake by thyroid.

in fasting blood glucose even after four weeks of cortisone therapy of 200 mg. daily. In another patient glucose tolerance was normal after 13.75 gm. of cortisone over a four-month period. Three patients had traces of glucose in the urine in single specimens of many examined.

Urinary 17-ketosteroids were determined before and during treatment in two patients. There was an increase in 17-ketosteroid excretion in both during therapy.

Tissue culture studies of Hodgkin's nodes removed by biopsy from two patients were tested against cortisone *in vitro*. Cortisone had no influence on the growth of Hodgkin's node. These included one patient who had an excellent subjective response to treatment.

The sedimentation rate decreased under therapy in five patients including one who became worse.

Bone Marrow Studies. The bone marrow in these cases showed definite changes during cortisone treatment. Perhaps the most im-

portant change was that which was observed in those patients with hypocellular marrows. Usually by the seventh day of therapy, and always by the twentieth day, there was a moderate to marked increase in cellularity. This increase was progressive during treatment and extended to the twelfth week. Observations after this time were not made. Similar increases in cellularity also occurred in those patients with normally cellular marrows. In one case in which the marrow was fibrotic as well as hypocellular there was an increase of cellularity on the fourteenth day of therapy at which time there was a marked decrease in fibrous tissue.

The initial increase in cellularity was due to normoblastosis or to erythroblastosis and normoblastosis. This was usually followed with a more marked erythroblastosis and exaggeration of the normoblastosis. Later, by the fourth to seventh week of treatment, the increase in cellularity was due to proliferation of granulocytic elements and restoration of a more nearly normal white blood cell/red blood cell ratio resulted.

In five of the six cases studied a substantial increase in reticulum cells occurred by the seventh or fourteenth day of treatment. This increase was sustained in three during the entire period of observation but in two the increase was not apparent at the third or seventh week of treatment but was noted at the seventh and twelfth weeks, respectively. Changing numbers of reticulum cells did not appear to be related to changing numbers of other cell types with the possible exception of megakaryocytes.

Increased numbers of megakaryocytes occurred on the seventh or fourteenth day of treatment. This change persisted throughout therapy and in two cases a further increase was noted at the third or seventh week of treatment. Associated with this increase in megakaryocytes was the appearance in three cases of agranular, large multinucleated cells resembling immature megakaryocytes. These may have been Reed-Sternberg cells. Also associated with the increase was a morphologic change in the megakaryocytes in which inclusions were observed in the cytoplasm. These were thought to be engulfed red or white blood cells. Still another change was vacuolization of the cytoplasm which in a rare instance suggested that the cell was fat-laden.

Another characteristic change was noted in the initial lymphocytosis. During the seventh to fourteenth day of therapy there was a decrease in the lymphocytes to normal. There was no subsequent increase in lymphocytes during treatment.

Changes in numbers of eosinophils were noted in all but two cases. There was an increase of both mature and immature eosinophils by the seventh or fourteenth day of treatment. The increase in mature forms exceeded that of immature forms. Usually, one week after the maximum increase in mature eosinophils there was a decrease to numbers in excess of the pretreatment levels.

Changes in the granulocytic series were most dramatic at the fourth to seventh week of treatment at which time marked proliferation of granulocytic elements occurred associated with a differential shift to the left.

In general bone marrow changes could not always be correlated with the findings in the peripheral blood. It is significant, however, that it was necessary to give few transfusions after the institution of cortisone treatment in a group which ordinarily would require many. It is possible that stimulation of the bone marrow by the hormone was responsible for this fact.

UNDESIRABLE EFFECTS OF THERAPY

Side effects were varied and required temporary cessation of treatment in one patient because of a convulsion. One patient bled from a gastric ulcer due to Hodgkin's infiltration of the stomach. (Fig. 3.) Another patient who died eight days after cortisone therapy was discontinued had perforated gastric and duodenal ulcers on autopsy associated with Hodgkin's infiltration. Suppression of the normal healing process by cortisone may have played a role in these cases.

Rounding of the face was observed in all who received therapy for more than a month. Edema of the lower extremities occurred in four. In two patients the edema was marked and was due at least in part to lowered serum proteins and severe abdominal nodal involvement. A low sodium diet in one patient produced a favorable response while therapy was continued but the edema later recurred.

Two patients developed hypertension to levels of 160/100 to 160/110. In one the hypertension reverted to normal while under therapy. In the other it persisted for a week after therapy was discontinued. Three patients developed severe acne of the face and trunk.

Muscle weakness increased in the two patients who became worse under therapy. The relation-

ship to therapy is difficult to evaluate in these patients. In two other patients muscle weakness appeared to be related to cortisone therapy. In three patients there was an initial increase in strength which regressed decidedly when dosage was diminished to 100 mg. three times weekly suggesting a rebound effect.

In one patient a grand mal seizure occurred while he received cortisone therapy. The cause of this convulsion is obscure. There was no change in blood pressure, blood volume, electrolyte disturbance or renal involvement that could be correlated with this occurrence. Therapy was temporarily discontinued. When cortisone was resumed, the convulsion did not recur.

Impairment of wound healing while therapy was continued occurred in one patient at the site of an axillary node biopsy. Lymphorraghia developed. The wound edges failed to unite and granulation tissue did not appear. This patient received testosterone propionate, 25 mg. intramuscularly daily, but it was only with cessation of cortisone dosage that healing ensued.

Reduction in dosage to 300 mg. of cortisone weekly was attempted in three of the patients who showed a good subjective response. All three relapsed and again improved when daily dosage of 100 mg. of cortisone was resumed.

COMMENT

That the patients selected for therapy represented severe and rapidly progressive forms of Hodgkin's disease is attested by the clinical findings, the course and the fact that six of the ten patients comprising the present study died in the four months that it was under way. None of the deaths can be attributed to cortisone therapy.

The effects of cortisone which have been observed were non-specific. They consisted chiefly in suppression of manifestations of toxicity and inflammation such as fever, anorexia, pain and increase in sedimentation rate. A feeling of well-being and euphoria was prominent in most cases. Unlike what has been observed in the leukemias true remission of the disease was not achieved in any case. In several there is little doubt that some inhibition of the rapidity of the course was effected. Essentially, as has been commented upon by Mote,[31] this represents suppression of the reaction of tissues to injury. Addition of nitrogen mustard to the therapy produced no additive effect. Nitrogen mustard was tried in seven patients after the institution of cortisone. In only one did improvement result. The impression was gained that in some cases the toxic effects of nitrogen mustard on the gastrointestinal tract were alleviated by the concomitant use of cortisone. This observation will be studied further.

In general it can be said that the effects of cortisone are inferior to roentgen therapy and nitrogen mustard. Both of these agents have produced regression of Hodgkin's disease after cortisone failed.

Manifestations of Hodgkin's disease which are mitigated by cortisone are fever, malaise, toxemia, anorexia, increase in sedimentation rate and weight loss. These are now well recognized responses of the body to non-specific injury or to stress, as admirably demonstrated by Selye's important contributions.[29] The mechanism of the elimination of these non-specific manifestations of the response of the body to stress by means of cortisone is unknown.

Stimulation of maturation of bone marrow elements by cortisone occurred in all cases, including those patients with leukopenia and anemia. This suggests that cortisone may have a limited field of application in this disease when roentgen therapy and nitrogen mustards are contraindicated because of marrow hypoplasia and leukopenia. In view of the symptomatic improvement induced by cortisone it may also be indicated in some debilitated patients in conjunction with other more specific measures.

SUMMARY

Ten patients with advanced Hodgkin's disease were treated with cortisone for periods varying between two weeks and three months. There was considerable but transient subjective improvement in seven. Fever subsided to normal in three.

Three patients became worse under therapy, all of whom died. In none was the unfavorable course attributable to the hormone.

In only one instance was significant regression of nodal or parenchymal involvement seen. In another patient considerable diminution of a postauricular mass occurred under cortisone therapy twenty-five days after a course of nitrogen mustard. The role of cortisone in this situation is debatable.

Studies of total body potassium with K^{42} showed a significant decrease in four of six patients which was not reflected by the plasma potassium level.

Depression of thyroid activity was found in five of six patients as manifested by decrease in radioiodine uptake.

Serial studies of the bone marrow regularly showed a stimulation of marrow elements by cortisone with marked increase in cellularity by the twentieth day of treatment. This was not always correlated with the findings in the peripheral blood.

Little effect was noted on eosinophils, blood volume or carbohydrate metabolism as a result of cortisone. The sedimentation rate fell in five patients in whom serial observations were made.

Relapses following reduction in dosage to 300 mg. weekly occurred in three patients in whom this was attempted. All three regained the previous limited improvement on restoration of 100 mg. daily dosage.

Undesirable effects were edema in five and rounding of the face in eight, acne in three, weakness in three following reduction in dosage, and hypertension in two. Generalized convulsions occurred in one. Gastrointestinal bleeding from a gastric ulcer due to Hodgkin's infiltration occurred in one. Another patient at autopsy eight days following cessation of cortisone therapy had perforated gastric and duodenal ulcers. He had had no symptoms referable to his gastrointestinal tract either before or after the perforation, unlike the case reported recently by Habif et al.[30]

We conclude from these observations that cortisone produces symptomatic improvement in some cases of advanced Hodgkin's disease. Other than reduction of fever and sedimentation rate, objective changes are few. There is little or no effect on the neoplastic process. True remission was not achieved with this hormone in any of the ten patients treated.

Acknowledgment: Acknowledgment is made of the cooperation of Irvin J. Cohen, M.D., Chief of Professional Services, and Mr. Sidney Shapiro of the Medical Illustration Department.

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Serum Complement in Acute Glomerulonephritis and Other Renal Diseases*

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THE activity of serum complement (C′) has been studied in various diseases in an attempt to accumulate evidence of antigen-antibody reactions. In acute glomerulonephritis several investigators have reported a decrease in serum complement early in the course of the disease.[1–4] In acute rheumatic fever similar reports of a decrease of serum C′ have not been confirmed[5] when the spectrophotometric technic of Mayer et al.[6,7] was employed. Indeed, an increase in the concentration of C′ was found in rheumatic fever and in many other acute and chronic inflammatory illnesses such as pneumonia, Hodgkin's disease and pulmonary infarction. The purpose of the present study is to determine the serum C′ in acute nephritis and other renal disturbances with this method.

METHOD

Blood was obtained from patients on the wards of the Babies Hospital and the Presbyterian Hospital, New York City, and the Cincinnati Children's Hospital. Serum was stored at −50°C. The materials, methods and calculations for the determination of serum complement are those of Mayer et al.[6,7] and have been summarized previously.[5] With this procedure the average normal human serum complement levels were found to be 38 ± 4, 50 per cent hemolytic units, in fifty normal individuals.[5] Subsequent determinations in normal individuals have confirmed this range irrespective of age (after six months) or sex.

The diagnosis of acute nephritis or other renal disease was made after consideration of the history, physical state of the patient and examination of the urine and blood at frequent intervals. Patients were observed for a follow-up period of several months to two years for confirmation of presumptive diagnoses and to differentiate acute from chronic nephritis. In some instances, as indicated hereafter, equivocal diagnoses remain.†

The date of onset of the disease is taken as the first manifestation of an abnormality which is compatible with acute glomerulonephritis (viz., severe headache, blurring of vision, edema of face or ankles, gross hematuria or orthopnea) and which is followed within a day or two by other manifestations of the disease (viz., other of the foregoing symptoms and signs, medical examination revealing elevated blood pressure or edema, nitrogen retention and abnormal urine constituents). In almost all instances of acute glomerulonephritis there was a history of a preceding upper respiratory tract infection or definite elevation of the antistreptolysin "O" titer.

RESULTS

Serum Complement in Acute Glomerulonephritis. Table 1 lists the C′ levels in thirty patients seen at various periods of time after the onset of acute glomerulonephritis. During the early days of the disease the serum C′ level is low. Of eighteen patients observed during the first ten days a distinctly low level (less than thirty-one 50 per cent hemolytic units per ml. serum) was present in all but one. The one patient (Case 14) with an initial low normal value of 33 units had a rash which was attributed to penicillin sensitivity. Subsequently there was an elevation of C′ in keeping with previous experience that this

† For aid and data in the follow-up of patients the authors are indebted to members of the Nephritis-Hypertension Clinic of the Presbyterian Hospital, Drs. D. W. Atchley, G. P. Bradley, S. E. Bradley, E. N. Loeb, R. F. Loeb and G. A. Perera, and to Dr. J. Yamazaki at the Cincinnati Children's Hospital.

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usually occurs with drug allergy much as it does with most inflammatory reactions.[5,8]

The serum C′ of twelve additional patients was first determined after the tenth day of the disease. Only five of these had C′ levels of 30 units or below.

twenty-one, nine continued to have low C′ levels and thirteen had normal or elevated C′ levels. One patient (Case 15) had an unexplained normal C′ and then a return to low levels; five patients were not studied during the second ten-day period. Therefore, somewhat

TABLE 1

SERUM COMPLEMENT (C′) IN ACUTE GLOMERULONEPHRITIS*

Case No.	Days after Onset									Remarks
	2–4	5–7	8–10	11–14	−21	−28	−35	−42	−49	
1	18	46(*a*)		35						(*a*) Periapical abscess end of 1st wk.
2(*b*)	11	10		9,14	20	27,26	38	40		(*b*) See Fig. 1, E.F.
3	10	10								
4	10	18	12		11					
5	17	32		43						
6	17	47		36	30	28				
7		21,21			39					
8		29				48				
9		30	43		57					
10		15								
11		16	18,18		20					
12		0	12	20						
13		19		30						
14		33(*c*)	55	38						(*c*) Penicillin rash
15			19		40,19		31		33	
16			26							
17			26		0(*d*)	31	35	34		(*d*) Clinically worse; 42 in 10th wk.
18			28(*e*)			23		26		(*e*) Left otitis and hemolytic streptococcal pharyngitis
19				34	39					
20				37	40	49,54	50		51	32 in 11th wk.
21				54(*f*)	50	73,62	65		61	(*f*) Concurrent rheumatic fever
22					0,0			0		0 in 8th wk.; 0 in 12th wk.; 40 after 1 yr.
23					30,31	44				
24					38	38				
25					39	34				
26					36	37	39			
27					14			24		
28					14,24		63(*g*)	81	65	(*g*) Developed thyrotoxicosis
29							38	47	41	39 in 8th wk.
30							30	41		

* 50% hemolytic units of C′ per ml. serum in relation to duration of disease.

The C′ level returns to normal during the course of the disease and this return is often rapid. In the eighteen patients seen less than ten days from the onset of acute nephritis normal or elevated levels developed in eight by the end of the second ten-day period (i.e., by the third week of illness). Six patients continued to have low C′ levels and in four cases no C′ determinations were made during the second ten-day period. Of the twenty-eight patients with adequate C′ determinations during days eleven to more than half the individuals had a normal C′ by the end of the third week.

The elevation of C′ above normal in several patients could be correlated with intercurrent inflammatory illness[5,8] such as apical tooth abscess (Case, 1) penicillin rash (Case 14) or concurrent rheumatic fever (Case 21). Classical thyrotoxicosis developed in one patient (Case 28) while under observation for acute nephritis. In a few instances of thyrotoxicosis the serum C′ concentration has been found to be elevated.

Another patient (Case 18) had a hemolytic streptococcal infection of the pharynx and an exacerbation of otitis media. The C′ concentration, although not above 30 units per ml. at the time, was possibly elevated above what it might have been with uncomplicated acute

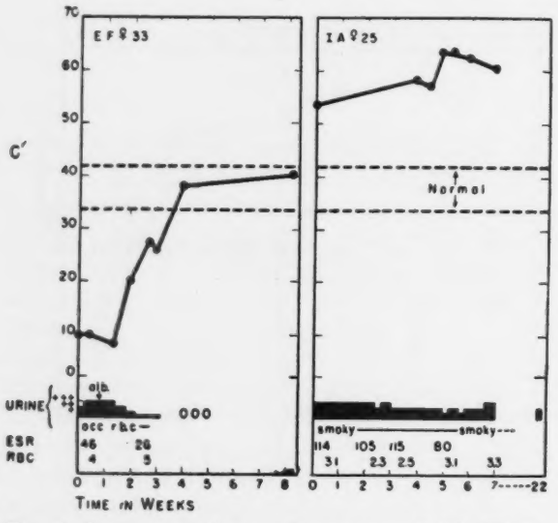

FIG. 1. Serum complement in acute nephritis (E. F., Case 2) and chronic nephritis (I. A., Case 33). Serum complement (C′) in 50 per cent hemolytic units per ml. serum; time in weeks after admission to the hospital.

nephritis since a slight fall occurred subsequently. It is apparent that in most instances the various inflammatory reactions, which have apparently caused an elevation of serum C′ in previous studies, continue to do so despite the tendency toward a low C′ early in acute nephritis.

There was no correlation between the time of disappearance of abnormal urinary findings and the return of low serum C′ to normal values. The C′ became normal before the urine did in many instances while in some cases the low C′ persisted for an unusually long period of time without any apparent difference from other patients in the clinical state of the individual. Serial C′ determinations are charted in relation to other findings in one patient, Case 2, patient E. F. (Fig. 1.)

Serum Complement in Subacute or Chronic Glomerulonephritis. Eleven patients with subacute or chronic glomerulonephritis were observed for varying periods of time. Of these six (Cases 31, 33, 35, 36, 39 and 40) had definite chronic glumerulonephritis. (Table II.) Another patient (Case 41) died in uremia with a history suggesting either hypertensive nephrosclerosis or chronic glomerulonephritis. The remaining four patients (Cases 32, 34, 37 and 38) had had what appeared to be an initial attack of glomerulonephritis. There were no data available on these patients preceding the apparent onset of the disease. The disease continued without evidence of diminution of abnormal urinary constituents for four to eight months. The term "subacute" glomerulonephritis is therefore used as a convenient clinical designation for this situation since the chronicity of the disease does not appear sufficient at this time to characterize the illness as chronic glomerulonephritis. In all but two cases the initial determination of serum complement concentration showed slight to marked elevations. In most instances the onset of the clinical picture was similar to that of the patients with acute glomerulonephritis. The serum C′ of patient I. A. (Case 33) is also charted Figure 1). One patient (Case 31) was seen in the second week of the disease with slightly elevated serum C′ of 46. The absence of a low serum complement in chronic nephritis and the nephritis associated with toxemia of pregnancy has been reported.[3,9] In contrast two patients in the present study with "subacute" nephritis (Case 32 and 38) had persistent low serum complement levels. It is of interest that two other patients (Cases 31 and 36) after initial slightly elevated levels developed the nephrotic phase of chronic glomerulonephritis. A reduction of plasma proteins and a heavy lipemia occurred in both instances. These changes may have affected the complement levels which fell to abnormally low values. Although comparable dilutions of serum were used as blanks in the spectrophotometer, the technical difficulties of measuring absorption of light in the presence of lipemic and turbid serum are sufficient to throw considerable doubt on these values.

Serum Complement in Other Nephropathies. Eleven patients with various kinds of renal disease exclusive of acute or chronic glomerulonephritis were studied. The results of complement determinations in these patients are presented in Table III. A very transient heavy albuminuria and hematuria in Case 42 accompanied left lower lobe pneumonia. The complement initially was high normal and later became markedly elevated. Acute pyelonephritis in Case 43 was accompanied by a high serum complement. Toxic nephritides due to carbon tetrachloride,

bacitracin or other toxins are also associated with high serum complement levels (Cases 44, 45, 46 and 47). In severe shock following induced abortion (Case 48) anuria and uremia developed. The patient was extremely ill and the serum complement was somewhat reduced as has been described in moribund states. With recovery the serum complement rose to elevated levels. Two of three children with "lipoid" nephrosis presented low complement levels (Cases 49 and 51) and the third (Case 50) demonstrated an elevated level. In the nephrotic syndrome associated with intercapillary glomerulosclerosis and diabetes (Kimmelstiel and Wilson syndrome) a single determination was slightly above normal.

TABLE II

SERUM COMPLEMENT (C′) IN "SUBACUTE"* AND CHRONIC GLOMERULONEPHRITIS†

Case No.	Time after Onset during Which C′ Was Determined	Serum Complement Values—50% Hemolytic Units	Remarks	Months' Duration of Definitely Abnormal Urinary Findings at Last Examination
31	2 to 9 wk.	46,38,29,27,23	Developed nephrotic syndrome in 4th wk.; chronic glomerulonephritis	18
32	3 to 4 wk.	14,15,17,26	"Subacute" glomerulonephritis	8
33	1 to 7 mo.	53,58,57,63,63,62,60,53	Chronic glomerulonephritis (Fig. 1, I. A.)	10
34	4 to 8 wk.	59,53,52,50,53	"Subacute" glomerulonephritis	5
35	7th wk.	43	Chronic glomerulonephritis	28
36	3 to 4 mo.	47,13,15,21,15	Developed nephrotic syndrome; chronic glomerulonephritis	14
37	4th mo.	46	"Subacute" glomerulonephritis	4
38	4 to 6 mo.	5,5,5,0,0,5	"Subacute" glomerulonephritis	10
39	1 yr. known nephritis	82,69	Uremia; died 1 mo. later	24
40	14 yr. known nephritis	52	Uremia and heart failure; temporarily recovered	14 yr.
41	2 yr. known hypertension	55	Uremia; died 3 days later	.....

* "Subacute" is used for cases which by virtue of duration cannot be categorized with certainty as either acute or chronic glomerulonephritis.

† 50% hemolytic units of C′ per ml. serum in relation to the duration of disease.

COMMENTS

The results, using the spectrophotometric method for determining the 50 per cent hemolytic unit in the presence of calcium and magnesium, confirm previous findings[1–4] of a low serum complement (C′) early in the course of acute glomerulonephritis. Further confirmation of the earlier studies has more recently been obtained by Wedgewood and others,[27] and Weinstein and Lecca.[28] It was considered important to substantiate previous reports since claims that the serum C′ is low in rheumatic fever, by workers who employed double dilution methods and usually read complete hemolysis, have not been substantiated using the newer method of titration.[5] In addition, very few of the published studies of complement levels have used technics which permitted the detection of amounts of C′ significantly in excess of the normal. In our experience this finding occurs in many inflammatory conditions and is far more commonly encountered than a low C′.[5,8] In about 1,500 sera from a wide variety of patients a low C′ was found with consistency only in early acute nephritis and lupus erythematosus disseminatus. In addition, one of two patients with serum sickness, two of ninety-five patients with rheumatic fever and several extremely ill individuals (viz., terminal staphylococcal pneumonia) exhibited diminished amounts of C′ in the serum. Acute glomerulonephritis and rheumatic fever, both non-suppurative sequelae of infection with hemolytic streptococci, have certain biologic differences which have been emphasized by Seegal and Earle.[10] In the markedly dissimilar variation of the level of serum complement in the

two diseases another biologic difference is evident.

The significance of the low C′ in acute nephritis has been a matter of speculation. Generally most authors[2–4] view the low C′ as a manifestation of an antigen-antibody reaction *in vivo*, similar to the complement-fixing potency of antigen-antibody reaction *in vitro*, as observed by Bordet and Gengou[11] in 1901. Several analogies may be drawn from experimental work to lend substance to this hypothesis. Ogawa and Sato demonstrated that the onset of nephrotoxic nephritis in rabbits is associated with a fall in serum complement.[12] Schwab et al. described a similar fall at the time antibodies appeared and renal lesions developed in experimental serum sickness in rabbits.[13] There is a mass of data, much of it conflicting, on the fixation of complement *in vivo* during anaphylaxis.[14,15] In studies with Benacerraf[16] we have induced anaphylactic shock passively in guinea pigs by the methods of Kabat and his coworkers.[17,18] When 15 μg. of anti–egg albumin nitrogen are used for sensitization, severe or fatal anaphylaxis may occur without any perceptible diminution of serum complement. On the other hand, with increased amounts of antibody (viz., 600 μg. antibody N) anaphylaxis is also severe or fatal and complement levels fall dramatically. This is in accord with the *in vitro* findings of Osler et al.[19] that the amount of C′ fixed has a rough correlation with the amount of antibody present.

TABLE III

SERUM COMPLEMENT (C′) IN OTHER NEPHROPATHIES AND CONDITIONS SIMULATING ACUTE GLOMERULONEPHRITIS

Case No.	Day of Illness	C′ 50% Units per ml. Serum	Diagnosis	Urine Findings
42	2	44	Left lower lobe pneumonia	Albumin 4 plus, RBC loaded, few WBC; cleared after 1 wk.
	7	63		
43	14	60	Pyelonephritis due to B. coli and Staph. aureus hemolyticus	Albumin 3 plus, 40–60 RBC, few WBC
44	10	58	Nephritis and mild hepatitis due to carbon tetrachloride	Albumin 3 plus, many RBC, 2–4 WBC, many casts, clearing in about 1 wk.
45	9	57	Nephritis due to ? carbon tetrachloride; elevated blood urea nitrogen	Albumin 4 plus, rare RBC and WBC, clearing gradually after 3 wk.
	21	90		
	28	72		
46	22	80	Lower nephron nephrosis due to undetermined exogenous poison	Albumin 4 plus, clearing gradually over 6 wk.
47	11	51	Nephrosis due to bacitracin	Albumin 4 plus, gradually clearing in 2 wk.
48	? 5	29(*a*)	Lower nephron nephrosis, shock and transient uremia following induced abortion; no infection	Albumin 2 plus, 20–30 RBC, occasional WBC
	22	66		
	26	56		
	33	53	(*a*) = almost moribund	
	40	53		
49	45	21	"Lipoid" nephrosis	Albumin 4 plus, occasional WBC
50	±1 yr.	62	"Lipoid" nephrosis	Albumin 4 plus, occasional WBC
51	10	25	"Lipoid" nephrosis	Albumin 4 plus, occasional RBC and WBC; no change
	17	39		
	24	29		
	31	22		
52	58	46	Diabetes mellitus, nephrosis, (Kimmelstiel-Wilson syndrome)	Albumin 3 plus; microscopic, negative

The low C′ in acute nephritis may be ascribed to mechanisms other than fixation of C′ by antigen-antibody reactions. The presence of C′ in the urine has been reported by Seifter and Ecker.[20] However, this was described in many different conditions associated with proteinuria and serum C was not measured at the same time. Since renal abnormalities other than acute nephritis (Tables II and III) are not usually associated with a diminution of serum C′, the loss of C′ in the urine does not seem to explain the low serum levels in acute nephritis. In addition, in this study and in that of Reader a

low C′ level could not be correlated with the presence of the proteinuria of acute nephritis. Inhibition of C′ activity by substances such as large doses of γ-globulin may cause a reduction in the measurement of serum C′.[21] This may well explain the low C′ of lupus erythematosus disseminatus in which an increase in serum globulin is common and the serum exhibits anticomplementary activity. However, these abnormalities do not usually occur in the serum of patients with acute nephritis. Finally, a deficiency in the production of C′ or one of its components may be suggested as a possible cause of the low C′ in acute nephritis. That this is unlikely is indicated by the rapid elevation of C′ in acute nephritis in response to concomitant acute inflammatory conditions (Table 1, Cases 1, 14, 18 and 21) or thyrotoxicosis (Case 28). It would thus appear most likely that the low C′ of acute nephritis is related to a rather massive and protracted antigen-antibody reaction following a streptococcus infection. The wealth of evidence related to this hypothesis has been reviewed elsewhere.[22–26]

Kellett and Thomson, and Reader have emphasized the relatively short duration of a low C′ after the onset of nephritis. In general agreement with their observations more than half the patients in this study showed a return to normal or increased amounts of C′ by the end of the third week. Kellett and Thomson suggested that C′ determinations may be used to help differentiate acute glomerulonephritis from exacerbations of chronic nephritis. With certain qualifications this would appear to be justifiable. However, two instances of nephritis which are apparently becoming of the chronic variety exhibited a low C′ and, as noted in several instances, associated inflammatory lesions have accompanied an elevation of serum C′ in acute nephritis. A few cases of anaphylactoid purpura with or without hematuria have exhibited high complement levels. The determination of serum complement remains a rather simple and useful laboratory procedure which may be of aid in the diagnosis of acute nephritis if the qualifications mentioned are considered.

SUMMARY

1. Previous findings of a low serum complement (C′) in acute glomerulonephritis have been confirmed using the method of Mayer et al. Of eighteen patients seen within ten days of onset of the disease all but one had levels below thirty-one 50 per cent hemolytic units of C′ per ml. serum.

2. Other nephropathies studied showed predominantly an elevated serum C′. These included chronic and "subacute" nephritis and various toxic and other renal lesions. In two instances of "subacute" nephritis persistent low C′ levels were observed. Sera from nephrotic patients occasionally exhibited a low C′ but the attendant turbidity makes C′ determination technically difficult.

3. The significance of the low C′ and the relation of an allergic process to the pathogenesis of acute glomerulonephritis is discussed.

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Acquired Hemolytic Anemia as the Presenting Syndrome of Lupus Erythematosus Disseminatus*

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IT is the purpose of this paper to present three cases of disseminated lupus erythematosus with the presenting syndrome of acquired hemolytic anemia, followed subsequently by the classic changes of the primary disorder. The second aim of the paper is to review the blood changes in disseminated lupus erythematosus to bring out the point that the causative mechanism of these abnormalities in many cases may be a secondary form of "hypersplenism"; consequently it is desirable to look for Hargraves' cells[1] in all patients with evidences of increased splenic activity.

The three cases to be described appeared to be almost classic examples of idiopathic acquired hemolytic anemia until further studies were made and the disease progressed.

TABLE I

PERIPHERAL BLOOD STUDIES IN THREE PATIENTS WITH ACQUIRED HEMOLYTIC ANEMIA DUE TO ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

Case	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Platelets	Reticulocytes	Spherocytosis	Anisocytosis	Macrocytosis	Poikilocytosis	Polychromasia	Nucleated Red Blood Cells	Sickling
I, M.A.	12/31/49	5.2	1.75	15.0									
	3/2/50	4.9	1.08	15.6		30							
	3/6/50	Splenectomy											
	5/29/50	3.9	1.2	27.0	N	9.6		MO		SL	MO	3	0
	1/16/51	14.6	4.8	8.9	N	1.4		SL					
II, G.F.	1/9/51	5.2	1.75	15.0	N	15		MO	MK	SL	MO		0
	3/21/51	13.1	4.44	8.8	N	1.0							
III, P.S.	8/12/49	3.8	1.06	8.6	212.0	7.8	MK	MO	SL			1	

Abbreviations: N = normal; SL = slight; MO = moderate; MK = marked.

CASE REPORTS

CASE I. M. A., an eight and a half year old Mexican female, became ill in December, 1949, with fever, anorexia, skin pallor, cervical adenopathy and weakness. There was minimal arthralgia. Family and past histories were noncontributory. A physician found her to be dyspneic and pale. The spleen was felt at the iliac crest and the liver was down several finger-breadths. Hematologic data are given in Table I.

Symptoms persisted until February 3, 1950, when the patient was admitted to the hospital. Her hemogram and physical status were unchanged except for fever of 102° to 103°F. Red blood cell fragility was normal. Urinalysis showed 2 plus albumin and 4 to 6 red cells per high power field. Bone marrow examination revealed marked erythroid hyperplasia of the normoblastic type and normal myelopoiesis with a reversed myeloid-erythroid ratio. (Table II.) The patient received several transfusions and antibiotic therapy. On March 2nd her bilirubin was 7.4 mg. per cent and the direct Coombs' test

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positive. A diagnosis of hemolytic anemia was made. Following a 1,000 cc. blood transfusion her hemoglobin rose to 9.4 gm. Splenectomy was performed on March 6th. The immediate postoperative course was relatively uneventful. At operation a firm, smooth, glistening spleen

TABLE II

BONE MARROW DIFFERENTIAL COUNTS IN THREE PATIENTS WITH ACQUIRED HEMOLYTIC ANEMIA DUE TO ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

Case	Normal	I, M.A.	II, G.F.	III, P.S.
Cellularity	N	Inc.	Inc.	Inc.
Granulocytes	65.0	59.0	32.5	31.0
Lymphocytes	10.0		1.5	0.5
Monocytes	2.0			0.5
Estimated no. megakaryocytes	N	N	R	N
Megakaryocytes forming platelets	M	R	M	R
Pronormoblasts	4.0	2	4.5	2.5
Normoblasts	18	39	60	69.5
M/E ratio	4/1	1.4/1	0.5/1	0.4/1

Abbreviations: Inc. = increased; N = normal; M = most; R = reduced.

was found weighing 387 gm. which on cut section showed marked lymphoid hyperplâsia. The liver was enlarged. On microscopic study a diffuse reticuloendothelial proliferation with excessive iron pigmentation in liver, spleen and lymph nodes was found. On reviewing the splenic sections nine months later fibrinoid degeneration of the collagen was noted about the splenic arterioles with the characteristic onion skin change of lupus described by Klemperer.[2]

From March until her admission to Los Angeles County Hospital on May 24th the patient continued to be weak, febrile and anemic, with gradually increasing axillary adenopathy and hepatomegaly. On admission the patient was acutely ill with a temperature of 106°F., swollen, hot and tender elbows, stiff neck and evidence of pericarditis. Hematologic studies (Table I) showed, in brief, a hemoglobin of 3.9 gm. with evidence of acute hemolysis and leukocytosis. The urine was normal. Two blood cultures were positive for pneumococci. The patient responded fairly well to antibiotic therapy. While under treatment a right pleural effusion, swelling of the proximal interphalangeal joints of fingers of both hands and evidence of pericardial effusion developed. Although the patient improved somewhat clinically, the arthritis, pericarditis and effusions persisted. On July 15th, alopecia became marked and a transitory erythematous maculopapular rash appeared in the butterfly area which lasted only several weeks.

It was then believed that the diagnosis of disseminated lupus erythematosus was clear-cut. ACTH therapy was instituted with gradual clinical improvement and cessation of hemolysis. ACTH was stopped in September and the patient gradually relapsed. Lupus erythematosus cells were found only at this time.

Another course of ACTH* therapy was begun in October, 1950, and has been maintained until the present. All the patient's previous symptoms have disappeared. The only physical abnormality left, aside from evidence of Cushing's syndrome, is cardiomegaly. The patient's entire course is summarized in Figure 1.

Summary of Case I. An eight and a half year old Mexican female developed the typical pattern of acquired hemolytic anemia in November, 1949, with splenectomy in March, 1950, with no improvement. In May, 1950, arthritis, pericarditis and pleurisy with effusion developed. In July a transitory butterfly rash appeared for several weeks. Hargraves' cells were found in October. Most of the patient's symptoms persisted until she was given ACTH therapy.

CASE II. G. F., a seventeen year old Mexican female, was admitted to the Los Angeles County Hospital on January 8, 1951, complaining of exertional dyspnea for two weeks. She had been in good health until December 22, 1950, when she dyed her hair and the next day noted hive-like lumps scattered over her arms and hands. The lumps would last about a day and clear up only to recur in another area. These lesions occurred for a week. Mild arthralgia appeared in the shoulders, elbows and wrists for several days. On January 1, 1951, she became febrile, and noted tachycardia and exertional dyspnea.

Family history revealed that her mother and two sisters had been epileptics since childhood. Past history was non-contributory.

On physical examination the patient was found to be an acutely and chronically ill, jaundiced but well developed and well nourished female. Her temperature was 101°F., pulse 150,

* The ACTH (actrope) used has been very generously supplied by Mr. Richard Bruner of United Laboratories, Pasadena, Calif. It has been developed in conjunction with the U.S.C. Medical School and is assayed in animals by the Sayers' technic and in humans by the Thorn test.

respirations 22 and blood pressure 126/60. There were no cutaneous lesions. Fundus examination revealed many fairly well circumscribed, rounded superficial hemorrhages ½ to 1 disc diameter in size adjacent to the vessels, with a few scattered, irregular, superficial, whitish exudates ⅓ disc diameter in size. The lungs were clear with no evidence of effusion. Cardiac examination revealed the point of maximum impulse to be in the fifth intercostal space at the anterior axillary line. A grade 2 systolic murmur was heard in the pulmonic area. The liver was down 2 finger-breadths. The spleen was not felt. For detailed hematologic studies see Table I. The blood studies, in brief, revealed a typical hemolytic pattern with a hyperplastic marrow (Table II) and evidence of marked regeneration of all elements.

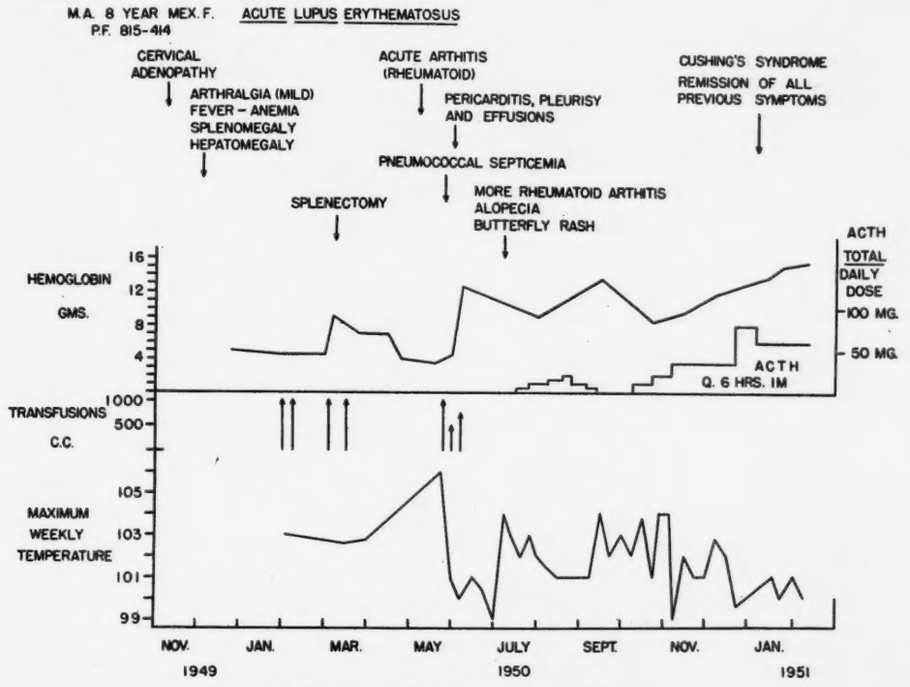

FIG. 1. Chart of clinical course of Case I.

The urine was dark brown in color but gave a negative test for bile. The urobilinogen test was positive in dilutions up to 1 to 64. The remainder of the urinalysis was within normal limits. Acid hemolysis test for paroxysmal nocturnal hemoglobinuria was negative. Red cell fragility test was normal. Serum albumin was 4.1 gm. per cent, globulin 2.8 gm. per cent and icterus index 43. Cold agglutination was negative. Wassermann and Kahn tests were doubtful. Coombs' test was positive by direct and indirect technics. Thymol turbidity was 6U and cephalin flocculation 1+. Chest x-ray was clear. Alkaline phosphatase was 4.9 u and the serum non-protein nitrogen 53 mg. per cent.

The patient received several transfusions. Hemolysis continued to be evident. Because of our experience with Case I a peripheral blood lupus erythematosus preparation for Hargraves' cells was made. This was positive on January 17, 1951. On January 19th small bilateral pleural effusions had appeared and by the following week these were more marked, and confirmed by a diagnostic tap. On January 24th ACTH therapy was begun (40 mg. per day by continuous intravenous infusion).[3] Within five days after start of therapy the patient became afebrile, the reticulocytes rose to 34 per cent and the hemoglobin also began to increase. The significant clinical features and course are summarized on the chart in Figure 2.

On February 7th early indications of Cushing's syndrome appeared. The icterus index had fallen to 10. A urinalysis on February 12th showed albuminuria with casts. By March 21st while on continued ACTH therapy the patient's hemoglobin was 13.3 mg., the urine was clear and the L.E. factor was no longer found.

Summary of Case II. A seventeen year old Mexican female became ill within twenty-four hours of using a hair dye. During the next few weeks the classic pattern of acquired hemolytic

anemia developed. Hargraves' preparation was made on peripheral blood which led to a correct diagnosis. Within the next few days bilateral pleural effusions developed and later nephropathy. No skin lesions have appeared to date. The patient responded well to ACTH therapy

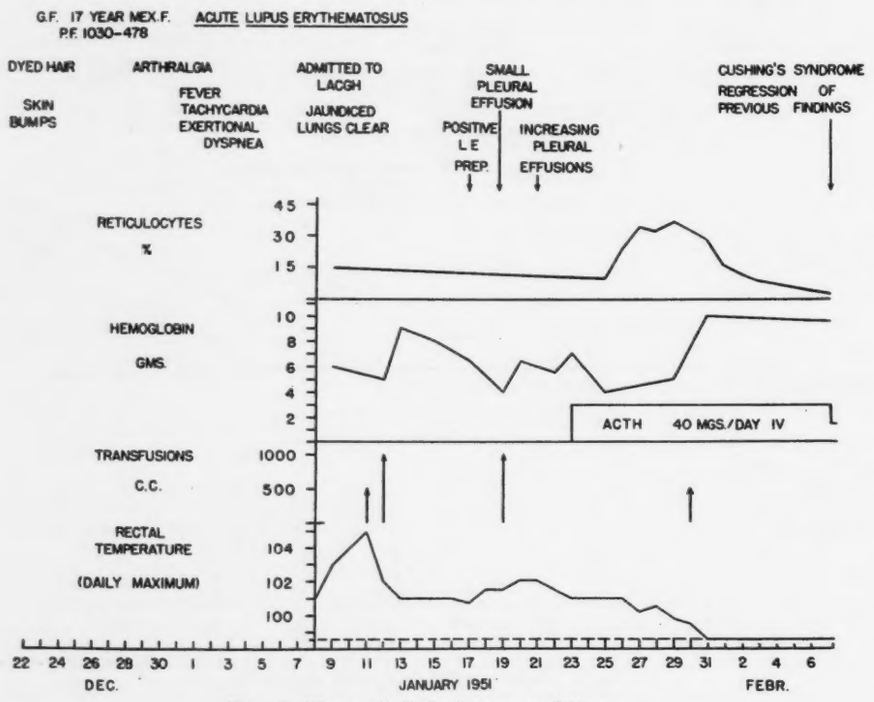

FIG. 2. Chart of clinical course of Case II.

and the L. E. factor was no longer found in her serum.

CASE III. P. S., a thirteen year old white female, was admitted to the hospital on July 23, 1949, complaining of lethargy, pallor, fever and vomiting for a few weeks prior to admission.

The past history revealed that she had had frequent headaches during the preceding four years. There had been recurrent nose bleeds for the past three years but no other bleeding tendencies. Convulsions had occurred in childhood. Her mother had had epilepsy when a girl. On physical examination the patient's temperature was 101°F., pulse 120, respirations 20 and blood pressure 124/0. The patient was a thin, pale, fairly well developed female thirteen years of age who was lethargic and confused. The skin was pale and sallow, with slight icterus. No skin lesions were noted on admission by several observers. There were ectatic vessels in Kiesselbach's area. Small, movable, firm lymph nodes were present in both anterior cervical chains, in the left posterior cervical area and in both axillas.

Fundus examination revealed several round and flame-shaped hemorrhages in each fundus, without exudates. The lungs were clear. On cardiac examination the left border of dullness was found to be 2 cm. beyond the mid-clavicular line with a grade 3 systolic murmur of maximal intensity over the pulmonic area. The liver was enlarged 2 fingerbreadths below the costal margin and the spleen 3 to 4 fingerbreadths. Bilateral ankle clonus was present. For detailed hematologic studies see Tables I and II. In brief, the patient had a hemoglobin of 3.8 gm. per cent with white count of 8,600 and evidence of hemolytic pattern, with hyperplastic bone marrow. On many occasions later the white count was as low as 2,700 to 3,500. Red cell fragility tests varied from normal to slightly increased. Bleeding time was two minutes and clotting time (Lee-White) six minutes. Clot retraction was normal. Direct Coombs' test was positive; Van den Bergh 4 mg. per cent, mostly indirect. Cold agglutination test was positive in 1 to 2,000 dilution. The serum albumin was 3.3 gm. per cent and globulin 4.0 gm. per cent. Electrophoresis showed 47 per cent gamma globulin as against 12 per cent normal. The serum non-

protein nitrogen was 34 mg. per cent. Doan's adrenalin test caused the hemoglobin to rise from 3.6 to 4.0 gm. per cent; the red count increased from 1.25 to 1.80, the white count from 10,000 to 12,400 and platelets from 180,000 to 192,000. Differential counts were essentially unchanged. The urine was dark brown with urobilinogen positive in 1 to 40 dilution; bile was not present. Microscopic examination showed 10 to 12 white cells per high power field with a few granular cases and rare (?) red cell cast. The blood Wassermann reaction was doubtful. Lymph node biopsy showed nonspecific inflammation.

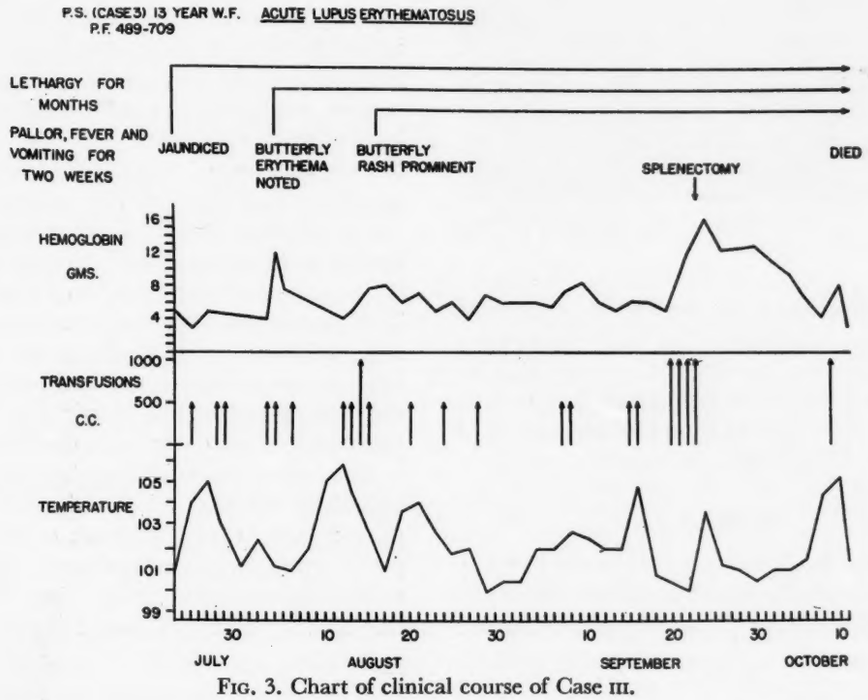

FIG. 3. Chart of clinical course of Case III.

The patient was given numerous transfusions, with hemolysis continuing. On August 5, 1949, a butterfly type erythema was first noted. On August 11th the patient was transferred to Los Angeles County Hospital, with a diagnosis of disseminated lupus, for ACTH therapy. Due to the small supplies available at that time she was given only 5 mg. every four hours without any effect on the course of the disease, as outlined in Figure 3.

On August 16th the butterfly rash became very prominent and a macular, erythematous, non-pruritic eruption spread over the chest, abdomen and back. This eruption lasted a few days and cleared, only to recur with minute vesicles. Her face became very edematous. Because of continuing hemolysis, which was threatening her life, splenectomy was performed on September 23rd. A large spleen weighing 610 gm. and one accessory spleen were removed. On section the follicles were prominent and 2 to 3 mm. in diameter. Microscopic study revealed classic lupus changes. Liver biopsy showed increased hemosiderin in the Kupffer cells. Lymph nodes were hyperplastic with peculiar necrotic areas.

Postoperatively the patient continued to show hemolysis and she expired on October 11th. At autopsy there was, in addition to the skin changes heretofore described, a 500 cc. pericardial effusion, with patchily thickened pericardium. No Libman-Sacks endocarditis was found. There were bilateral pleural effusions with thickened pleura. A small amount of ascitic fluid was present, with 40 cc. of pus in the splenic bed. There were no accessory spleens. The adrenals weighed 5 gm. together and appeared normal. The vertebral marrow was red and soft, and filled the entire body of the vertebra. Microscopic studies showed renal wire loop lesions and other changes compatible with lupus. The bone marrow was very cellular.

Summary of Case III. A thirteen year old white female presented herself with severe acquired

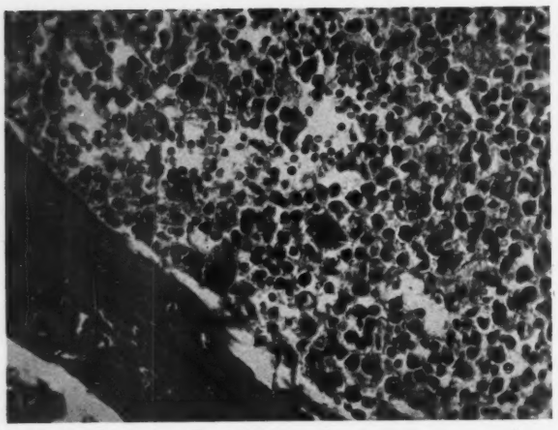

FIG. 4. Case III. Postmortem bone marrow section; note cellularity.

hemolytic anemia and two weeks later a minimal butterfly lesion was noted. The main therapeutic problem was the continuing hemolysis, for which splenectomy was performed but proved to be of no value. Postmortem studies confirmed the diagnosis of disseminated lupus.

COMMENTS

A review of the literature fails to disclose any previously reported cases of acquired hemolytic anemia as an initial or presenting manifestation of disseminated lupus erythematosus. Since acquired hemolytic anemia is thought to be an indication of "hypersplenism,"[4,5] the question arises as to whether the hematologic abnormalities of lupus could be explained by this mechanism. According to Doan and Weisman, the following changes may be due to increased splenic activity provided that the bone marrow appears hyperplastic:[4] leukopenia, thrombocytopenia and hemolytic anemia.

The occurrence of *leukopenia* is well known in this disease and is present in about half of the cases at some stage.[6] It should be noted that leukocytosis was present at least temporarily in our three cases. Although leukopenia may be present in the peripheral blood the bone marrow usually is hyperplastic, often with a shift to the left in the myeloid series.[27] Due to the associated hemolytic anemia the myeloid : erythroid ratio is reduced in spite of the relative increase in immature granulocytes. The marrow counts are similar to those reported by Weisman and Doan in panhematopenia due to "hypersplenism." The postmortem bone marrow is usually quite red and sections show it to be very cellular (Fig. 4) even without marked terminal hemolysis. Klemperer in his classic review noted no particular abnormalities in the marrow.[2]

The appearance of *thrombocytopenic purpura* as an initial manifestation of lupus has been reported many times. Purpura of a non-thrombopenic type may occur in disseminated lupus due to the diffuse vasculitis with increased capillary fragility. Lyon reports a case of proven thrombopenic purpura and leukopenia in a patient in whom disseminated lupus subsequently developed.[11] Others have described similar cases.[6,12,13] Unfortunately, the morphology of the megakaryocytes is not reported. Dameshek has shown that in idiopathic thrombocytopenic

TABLE III

STUDIES IN THREE PATIENTS WITH ACQUIRED HEMOLYTIC ANEMIA AND ONE WITH UREMIA DUE TO DISSEMINATED LUPUS SHOWING THE DIRECT RELATION BETWEEN ACTIVE HEMOLYSIS AND POSITIVE COOMBS' TEST

Case	Date	Hemoglobin	Non-protein Nitrogen	Icterus Index	Fecal Urobilinogen (mg./24H)	Hemolytic Index	Coombs' Test		L. E. Factor
							Direct	Indirect	
Normal					38–226	17–21	0	0	0
I, M.A.	12/31/49	5.2					+		
	3/2/50	4.9	30	14			+		
	10/1/50								+
	1/24/51	14.6	27	6			0	0	0
II, G.F.	1/21/51	7.0	53	43	580	165	+	+	+
	3/31/51	13.1	24	7	27	4.1	0	0	0
III, P.S.	8/6/49	3.6	34	36			+		
C.P.	1/24/51	8.6	100	5	25	6.5	0	0	+

Hemolytic Index[25] = (Milligram fecal urobilinogen daily/grams total body hemoglobin) x 100.

purpura due to "hypersplenism" the megakaryocytes are plentiful but do not form platelets.[14] Two of our patients with lupus had diminished platelets in the peripheral blood smear and study of their bone marrow revealed many megakaryocytes which were forming no platelets.

Some of the reported cases of thrombocytopenia in disseminated lupus also had leukopenia. Leukopenia is also frequently associated with hemolytic anemias,[4,15] Evans reporting this association in five of eleven cases of idiopathic acquired hemolytic anemia. Thus far, then, two of the three elements of hypersplenism are well known to occur in disseminated lupus.

Anemia is one of the classic features of disseminated lupus erythematosus. The three patients described herein showed evidences of *acquired hemolytic anemia*, with antibody formation, as a presenting symptom. Therefore, the triad of "hypersplenism"—leukopenia, thrombopenia and hemolytic anemia, with hyperplastic marrow—was fulfilled.

Evidence of increased hemolysis has been found in six of nine other patients with classic disseminated lupus. The rate of blood destruction varied and at times hemolysis was not in evidence, especially if the patient was uremic as in the case of C. P. (Table III.) The Coombs test in this case was negative. Evans has also noted the occurrence of a positive Coombs test in four patients with lupus but stated that tests for evidence of hemolysis were negative.[16] It should be pointed out that in hemolytic states associated with splenomegaly from malignancy or infection Coombs' antibodies are found; therefore, their presence in disseminated lupus only indicates that the hemolytic mechanism is secondary to the splenomegaly.

It is not our intention to enter the controversy regarding the mechanism of action of the syndrome of "hypersplenism" but simply to point out that "hypersplenism" may play a role in disseminated lupus erythematosus. It must be admitted that splenectomy fails to affect the blood picture in many instances of what is regarded as "hypersplenism" (as occurred in two of our cases of disseminated lupus) but this does not invalidate the concept, we believe.

SUMMARY

The syndrome of acquired hemolytic anemia is reported as an initial manifestation of lupus erythematosus disseminatus in three patients.

It is suggested that "hypersplenism" of the secondary or symptomatic type plays an important role as a causative mechanism of the hematologic abnormalities in disseminated lupus erythematosus, since leukopenia, thrombocytopenia with plentiful megakaryocytes not forming platelets, hemolytic anemia and a hyperplastic bone marrow may be found in many cases.

Splenectomy did not cause cessation of hemolysis in two of the three cases reported. ACTH was successful in producing a remission in two patients in whom it was employed, one after splenectomy failed.

All patients with evidence of "hypersplenism" should have routine studies for Hargraves' cells.

Acknowledgment: The author wishes to thank Paul Starr, M.D., Professor of Medicine, Chairman of the Department of Medicine, University of Southern California, for his helpful advice and criticism in writing this paper.

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Review

Sarcoidosis*

A Review with Twenty-four Additional Cases

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SARCOIDOSIS was so named in 1899 by Boeck,[1] a Norwegian dermatologist, who described nodular skin lesions which showed an epithelioid cell structure and which he believed to resemble sarcoma cells; hence the designation "sarcoid." Since that time many investigators have contributed to our knowledge of this disease but major credit for emphasizing its generalized nature goes to Schaumann.[2] In a number of articles he correlated the clinical and pathologic features and emphasized that the disease was a disseminated condition of the lymphatic and hemopoietic systems. Further investigation has revealed that there may be widespread involvement of practically every organ in the body.

Many excellent papers have recently appeared which relate in detail the historical aspects, clinical features and pathology of sarcoidosis,[3–5] and no attempt will be made to review the subject fully here. The purpose of this article is to report our observations of the clinical features and pathology of sarcoidosis based on our study of twenty-four cases observed at the Kennedy Veterans Hospital. While the series is not a large one, it differs from many others in that it does not represent a review of cases seen by a number of individuals but includes only patients actually observed by us over a period of years.

DESCRIPTION OF MATERIAL

These twenty-four cases represent all the patients with sarcoidosis seen in almost five years from July, 1946, to May, 1951. Histologic evidence of sarcoidosis in lymph nodes or skin was present in all but two patients. In some cases several confirmatory biopsies were obtained. In two patients biopsy substantiation was not obtained but the clinical course of each patient was so characteristic of sarcoidosis that these cases are included in the series. Because of similarity to the histopathology of tuberculosis, the criteria for the diagnosis of sarcoidosis are difficult to define. We included those cases which conformed to the criteria as listed in a definition of sarcoidosis by the Conference on Sarcoid of the National Research Council.[6] In selecting these patients for this report only those with generalized sarcoidosis were included. Patients who had only local sarcoid lesions were not considered in this study.

The plan for the clinical study included a complete history and physical examination for each patient. Routine referrals were made to the Ophthalmology Clinic where each patient was examined for evidences of ocular sarcoidosis. Dermatologic consultations were obtained only when patients exhibited skin lesions. The laboratory study included routine blood counts, urinalysis, serologic tests for syphilis, determinations of total serum proteins, albumin and globulin fractions, and serum calcium and phosphorus levels. Skin tests with purified protein derivative (PPD No. 1 and No. 2 if the former was negative) were performed. In addition, coccidioidin and histoplasmin skin tests were performed in nearly all cases. Routine x-rays of the chest, hands and feet were made. An electrocardiogram was taken routinely. A bone marrow aspiration was performed once in almost every case. If sputum was available, smears and cultures were examined for acid-fast bacilli; otherwise, gastric washings were done for this purpose. Patients were recalled to the hospital for follow-up examination at intervals.

* From the General Medicine and Hematology Section of the Medical Service and the Laboratory Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tenn. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion and policy of the Veterans Administration.

FIG. 1. Case 1. Lymph node biopsy showing typical early epithelioid granuloma; × 60.

FIG. 2. Case 1. Spleen showing epithelioid granulomas with central fibrinoid necrosis; × 100.

PATHOLOGY

The basic lesion in sarcoidosis is the epithelioid granuloma. (Fig. 1.) This is usually discrete and involves the lymphoreticular tissues, but any organ of the body may be the site of lesions. The pattern is often described as monotonous because the granulomas have a tendency to occur in "crops" showing the same stage of development. The lesions tend to remain discrete until the outline is blurred by fibrosis and hyalinization in the healing stage. This fibrotic healing begins after the earliest cellular lesion and at first encircles the granuloma with a thin layer of fibroblasts. The fibrous tissue develops into a compact layer which hyalinizes and finally forms a dense scar. Necrosis is not commonly a part of the lesion but a fibrinoid type of necrosis is encountered in some of the granulomas. (Fig. 2.) This type of necrosis was observed either in biopsy or autopsy material in seven of our twenty-two cases with tissue sections (32 per cent). The number of giant cells in the lesions is usually less than in tuberculosis, and both Langhans and foreign body type cells are encountered. Inclusions of Schaumann bodies and asteroids within the giant cells or free in the lesions are seen in some cases. Inclusion bodies or asteroids were present in three of our cases (14 per cent). (Fig. 3.) In older lesions a hyalin material similar in appearance to amyloid is present but it does not take specific stains for amyloid. (Fig. 4.) This has been termed paraamyloid by some writers, notably Teilum,[7] who considers it a product of the elevated globulin level present in this condition.

It should be noted that granulomas similar to the cellular sarcoid granuloma may be seen in a variety of other conditions, notably in lymph nodes associated with regional ileitis, chronic gallbladder disease and even in Hodgkin's disease. These, plus the granulomas seen in lesions produced by beryllium, histoplasma and medicated oils, are designated "sarcoid lesions" as distinguished from the generalized disease "sarcoidosis."

The autopsied cases of sarcoidosis have been reviewed by Pinner[8,9] who collected forty-three cases. In 1949 Ricker and Clark[6] found that the number had increased to sixty-two and reported twenty-two autopsied cases of their own. Since then single cases have been reported by Mann and Zimmerman,[10] Rosenthal and Feigen,[12] and Scotti and McKeown.[36] Nestman[11] reported two cases and Riley[5] ten additional autopsied cases, bringing the total number to ninety-nine cases, to which we wish to add three of our own.

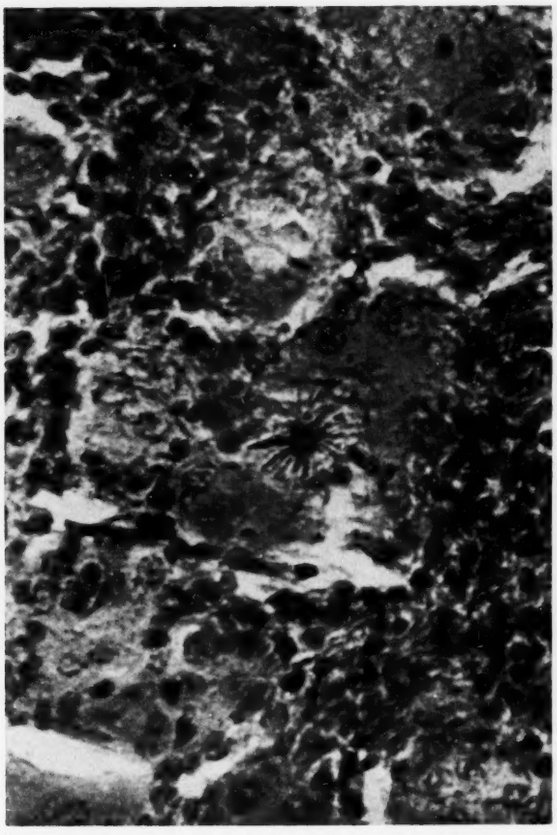

FIG. 3. Lymph node showing giant cell with asteroid inclusion body; × 200.

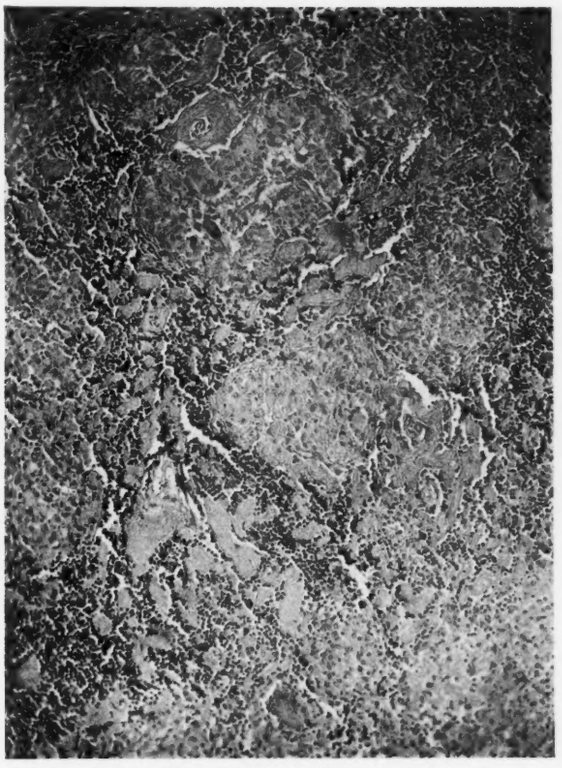

FIG. 4. Case III. Lymph node showing granulomas and sausage-shaped masses of amyloid-like material.

CASE REPORTS

CASE I. A twenty-eight year old Negro male had swelling, heat and tenderness in his right leg in 1944. This extended from the mid-thigh to the ankle and required incision and drainage following which the right leg remained weak and showed areas of hypesthesia. In early 1945 almost complete blindness in the patient's left eye developed, and this was diagnosed as chorioretinitis. He improved with fever therapy and vision returned in three months. About November, 1947, the patient noted exertional dyspnea and soon developed subcutaneous nodules over his buttocks. Chest x-ray showed diffuse bilateral pulmonary lesions. In early 1949 dyspnea had become progressively worse and was present at rest. Repeated study of sputums failed to show acid-fast bacilli. He was admitted to the Kennedy Hospital in April, 1949. Physical examination disclosed bilateral areas of healed chorioretinitis. The lungs showed an over-all impaired resonance and moist rales in both bases. The blood pressure was 104/78. The heart was normal. Liver and spleen were not palpable. Muscular atrophy and spotty hypesthesia were found over both legs. The left patellar reflex was hyperactive and left ankle jerk was absent. Despite atrophy of the right thigh and calf the deep tendon reflexes were hyperactive. At this time there was no significant lymphadenopathy and no skin lesions were present.

Blood count and urinalysis were normal. Repeated differential counts of leukocytes showed slight eosinophilia and occasional monocytosis. Total serum protein was 8.7 gm. per cent with a globulin of 4.7 gm. per cent. Smears of the sternal marrow were normal. The chest x-ray now showed a moderately dense generalized infiltration in both lung fields and hilar lymph node enlargement. On subsequent roentgen examinations these findings became progressively more marked. An electrocardiogram showed a pattern of cor pulmonale. First and second strength tuberculin, histoplasmin and coccidioidin tests were negative.

Shortly after admission enlargement of the left inguinal nodes developed and a biopsy showed sarcoidosis. By June, 1949, the patient had become so dyspneic that he was placed in an oxygen tent where he remained until his

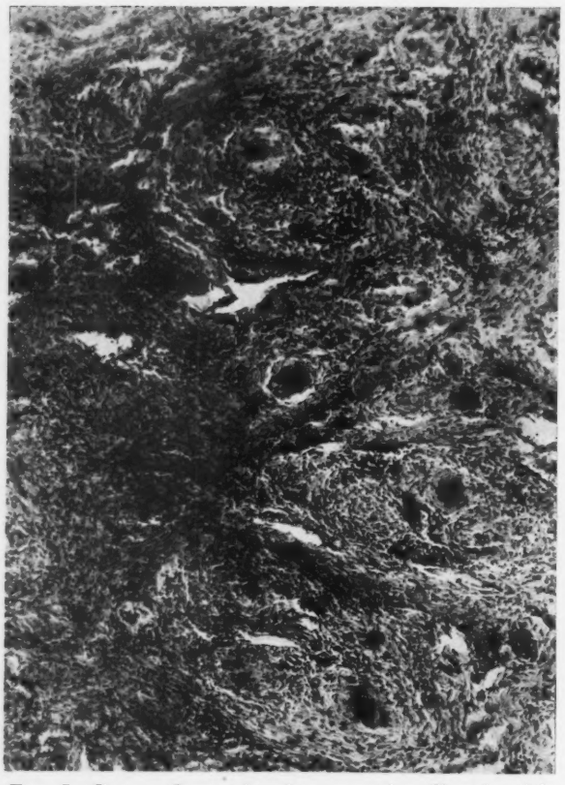

FIG. 5. Case I. Lung showing extensive fibrosis with scattered granulomatous foci; × 60. No alveoli are to be seen.

death in June, 1950. He could not be removed from the tent for more than a few minutes without becoming severely dyspneic and cyanotic.

Autopsy showed slightly enlarged cervical nodes. No skin lesions were present. The pericardium was covered by a layer of pinkish grey granulomatous tissue which extended over the parietal and visceral pleura bilaterally and into the upper mediastinum. A few membranous pleural adhesions were present bilaterally and there was a dense adhesion of the upper lobe of the left lung to the chest wall. There were 300 cc. of a cloudy yellow fluid in the left pleural cavity and 400 cc. in the right pleural cavity. The left lung weighed 770 gm. and the right 960 gm. These were greyish pink in color and covered by a layer of granulomatous friable tissue. They sectioned with the resistance of a dense, cirrhotic liver and revealed a scarred, whitish, red-streaked surface; no crepitancy could be palpated in any region. The enlarged discrete hilar nodes sectioned with resistance and presented a grey, homogeneous pattern. Microscopically, the lungs were a mass of hyalin fibrous tissue in which one found numerous sarcoid granulomas with many Langhans and foreign body giant cells. Only occasional areas of alveoli could be identified and the blood vessels showed marked thickening. (Fig. 5.) In sections from the hilar nodes the architecture was replaced by sarcoid granulomas. The pericardium was markedly thickened, densely scarred and heavily laden with granulomas. The heart weighed 420 gm. and showed right ventricular dilatation and hypertrophy (wall measuring 1.2 cm. in thickness) but otherwise was grossly normal. Microscopic section of the left and right ventricles revealed a few scattered small sarcoid granulomas. The spleen weighed 370 gm. and its surface and substance presented great numbers of discrete pinkish grey nodules measuring up to 4 mm. in diameter. The liver weighed 1,540 gm. and showed similar nodules. In both organs, microscopically, these nodules were formed by great numbers of granulomas and surrounding dense fibrosis. Some of the granulomas were undergoing central fibrinoid degeneration and giant cells were common. No caseation necrosis was seen. Representative sections of the spinal cord stained for myelin revealed some demyelinization of the lateral columns.

CASE II. In this thirty-six year old Negro male pulmonary infiltrations, hilar lymph node enlargement, dyspnea and electrocardiographic evidence of cor pulmonale developed over a three-year period prior to his first admission to this hospital. He had seven admissions to this hospital during which time his pulmonary lesions progressed, serum globulin increased and he developed sarcoid skin lesions proven by biopsy. His terminal admission was for marked congestive failure and he expired in September, 1950, six years after the onset of his illness. At necropsy the lungs had a combined weight of 1,520 gm., sectioned with resistance and revealed numerous whitish nodular areas throughout. Microscopically, there was extensive cellular and hyaline fibrosis in which scattered sarcoid lesions could be found. Sections of the hilar and abdominal lymph nodes revealed almost complete replacement by amyloid-like material. The heart weighed 440 gm. and the right ventricle was hypertrophied. The spleen, which weighed 100 gm., contained scattered hyalin nodules with a few remaining giant cells. The liver contained amyloid-like nodules but was not enlarged.

CASE III. This Negro male first had skin lesions and lymph node enlargement at twenty-

three years of age, four years prior to death. Both first and second strength tuberculin tests were negative. Chest x-ray showed nodular infiltrations in both lung fields and marked widening of the hilar shadows. He developed cystic changes in the phalanges and the left fifth metatarsal bone. Biopsies of a skin lesion and of an epitrochlear node showed typical lesions of sarcoidosis. While under study he developed a spontaneous left pneumothorax and expired in less than twenty-four hours. At autopsy the lungs had a combined weight of 1,660 gm. and showed apical emphysematous blebs. Sarcoid granulomas were demonstrated in the lungs, lymph nodes, spleen, liver and kidneys. There was right ventricular hypertrophy. This case was previously reported by one of us.[13]

COMMENTS

A critical analysis of the ninety-nine previously reported autopsied cases of sarcoidosis shows that in only thirty-nine could death be attributed directly to sarcoidosis (excluding the cases with pulmonary tuberculosis). Of these twenty-three died as a result of pulmonary involvement, six of cardiac involvement, seven of central nervous system or pituitary involvement, and three with overwhelming generalized sarcoidosis. The three autopsied cases herein presented died as a direct result of sarcoidosis, two with marked pulmonary involvement and cor pulmonale, while the third had pulmonary involvement with rupture of an emphysematous bleb and electrocardiographic evidence of cor pulmonale. Stained sections of the granulomatous lesions failed to reveal acid-fast bacilli and stains for amyloid (Cases II and III) were negative.

INCIDENCE

Sarcoidosis can no longer be considered a rare disease. Many large series of cases have been reported in the past ten years and, with an increasing awareness of the disease, more cases undoubtedly will be recognized in the future. The disease affects either sex equally although some studies point to a higher incidence in the female.[3,4] Our own series from a Veterans Administration hospital is, of course, heavily weighted in favor of the male and cannot be used as a true indication of the sex ratio. One of our patients was a colored female; all other patients were males. The disease is predominantly a disease of young adults and the ages of our patients varied between twenty-one and fifty-four years of age with an average age of twenty-nine years. Most recent American series have shown a marked predominance of Negroes, usually 80 per cent to 85 per cent of cases occurring in Negroes.[3,4] Of our own series of twenty-four cases, twenty-one were Negroes, an incidence of 88 per cent. Based on the comparison of white to Negro troops in the Army, Ricker[6] stated that sarcoidosis was seventeen times as frequent in the Negro. Our own figures based on the ratio of white to Negro admissions to the hospital indicate that sarcoidosis in this area is twenty-six times as frequent in the Negro as in the white patient.

CLINICAL MANIFESTATIONS

Because of the involvement of many organs, the clinical features may be protean. The most common manifestations are pulmonary involvement plus hilar and peripheral lymph node enlargement.

Peripheral Lymph Nodes. Enlargement of the peripheral lymph nodes is a characteristic feature of sarcoidosis. The nodes are non-tender, discrete and small to moderate in size. Only rarely do they exceed 2.5 cm. in diameter and usually they are smaller. In our series twenty-one patients (88 per cent) had enlargement of the peripheral lymph nodes at some time during the course of their illness. The lymph nodes of most patients were observed to regress during observation and sometimes to disappear completely. Occasionally the nodes remained enlarged, in one case until the patient's death (Case III). Three patients did not show peripheral lymph node enlargement. However, two of these patients had hilar lymph node enlargement demonstrated on chest x-ray. One patient had neither hilar nor peripheral lymph node enlargement. He was seen during only one admission, four years after the onset of his sarcoidosis, and it is possible that involvement of the peripheral lymph nodes had been present prior to our observation of this patient.

Thoracic Lymph Nodes. Enlargement of the hilar and mediastinal lymph nodes is also quite characteristic of sarcoidosis. This is sometimes massive and occurs early in the course of the disease, preceding x-ray evidence of pulmonary involvement. Twenty of our patients showed evidence of enlargement of thoracic lymph nodes, an incidence of 83 per cent. Like periph-

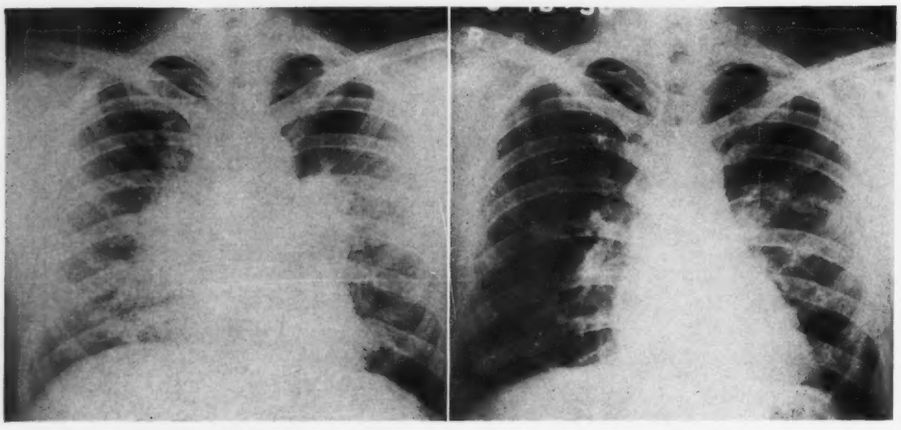

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FIG. 6. A, X-ray of the chest showing massive hilar lymph node enlargement with some fan-shaped infiltrations into both mid-lung fields; B, eleven months later there has been complete resolution.

eral lymph node enlargement, the thoracic node enlargement receded with time. The nodes may be quite large, the so-called potato nodes. It is probable that even without x-ray evidence of enlargement these nodes may be involved for it is well known that the nodes must enlarge considerably before the enlargement becomes apparent by x-ray. The enlargement is usually bilateral and symmetrical although on occasion it is predominantly unilateral and suggestive of tuberculosis. It is said that obstructive symptoms due to pressure of enlarged nodes are rare;[3] however, one of our patients (Case III) had marked compression of the bronchial tree with secondary emphysema. Spontaneous pneumothorax occurred because of a ruptured emphysematous bleb.

Lungs. The lungs are nearly always involved at some time during the course of the illness. Twenty of our twenty-four patients showed evidence of pulmonary involvement, an incidence of 83 per cent. However, three of the four patients without lung involvement had evidence of hilar lymph node enlargement. The only patient without either lung or hilar lymph node enlargement gave a previous history of cough and fever with the onset of his illness four years prior to our observation. It is possible that he had such involvement at that time.

The symptoms resulting from pulmonary involvement are variable. Some patients have few or no symptoms despite fairly extensive pulmonary lesions and this disparity between the symptoms and x-ray findings has been considered suggestive of sarcoidosis. However, in most patients with pulmonary involvement symptoms such as cough and dyspnea are usually present to a greater or lesser extent. With very marked involvement there is usually severe pulmonary insufficiency, although this is hard to dissociate from the accompanying cor pulmonale. One of our patients (Case I) had such severe dyspnea that he had to live in an oxygen tent for one year and any attempt to remove him from the tent for longer than a few minutes at a time resulted in progressively severe dyspnea and cyanosis. The physical findings in sarcoidosis are also variable and tend to be inconspicuous or slight when compared to the extent of involvement demonstrable by x-ray.

The x-ray findings may be classified into a number of types which represent phases in the natural history of the disease and which merge into each other. The types usually seen may be divided into (1) bilateral hilar lymph node enlargement without detectable lung changes. We believe that this might be the earliest evidence of intrathoracic disease. The condition may go on to healing from this point or more frequently it progresses to (2) bilateral hilar node enlargement with strand-like infiltration extending from the hilar regions into both lung fields. This infiltration progresses, and small nodular beading occurs along the strands with ultimate diffuse mottling similar to that seen in miliary or hematogenous tuberculosis. The hilar lymph nodes may become progressively enlarged during this time or they may gradually regress. (Fig. 6.) (3) Later there is diffuse pulmonary infiltration consisting of patchy coalescent densities. This is more pronounced in the mid-portion of the lung and less often in the

bases. The infiltration may also occur in the apexes causing great difficulty in differentiation from pulmonary tuberculosis. These densities are most frequently bilateral and symmetrical but occasionally may be asymmetrical and sometimes predominantly unilateral. (4) Finally, a stage of fibrosis and secondary emphysema with formation of bullae occurs. (Fig. 7.) Our observations would lead us to believe that this change is permanent with little possibility of recovery. As previously noted, one of our patients with secondary emphysema due to compression of the bronchial tree by enlarged hilar lymph nodes developed a spontaneous pneumothorax and died.

Tuberculosis occurs frequently in patients with sarcoidosis. Freiman[3] stated that 10 per cent of reported cases showed evidence of tuberculosis. Riley[5] noted that in 25 per cent of his cases active tuberculosis developed. Four of our patients (17 per cent) had concomitant tuberculosis. These patients were found to have positive cultures for acid-fast bacilli on at least one occasion. Two of these patients had negative tuberculin reactions and following treatment with streptomycin positive cultures could not be obtained although the clinical evidence of disease was uninfluenced. It is possible that both of these patients were developing superimposed tuberculosis which was controlled by streptomycin administration. The other two patients had positive tuberculin reactions and probably had active tuberculosis.

Skin. Ten of our twenty-four patients (42 per cent) had sarcoid skin lesions during the course of observation. This compares with an incidence of 7 per cent to 40 per cent in several other series.[4,5,14,15] There is no skin lesion which is pathognomonic of sarcoidosis although the type and location of the lesions may be suggestive. The lesions are usually in the form of nodules or papules. The number of individual lesions varies. There may be a large number but in some cases careful search was required to find three or four small nodules. There is a predilection for the extensor surfaces of the extremities, the chest, abdomen and eyelids or nose. Diffuse infiltrating plaques have been described but were not observed in this series. As a rule the lesions do not ulcerate but in one of our cases superficial ulceration did occur. (Fig. 8.) Occasionally there is scaling. Symptoms are generally lacking. Subcutaneous lesions may be found and these have frequently been referred to as lesions

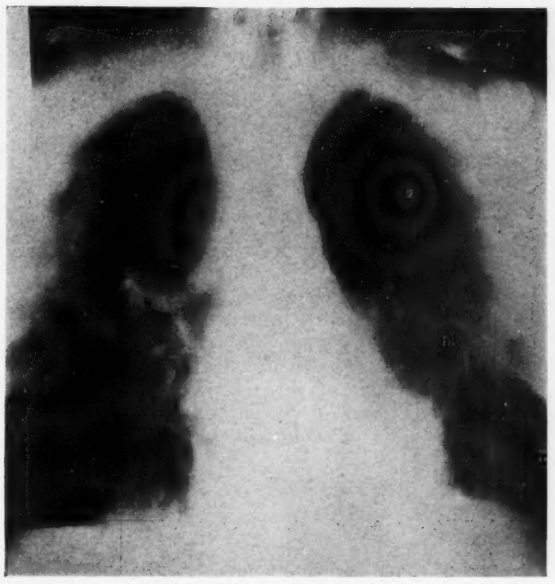

FIG. 7. A laminogram of the chest showing the extensive bulla formation.

of the Darier-Roussy type. The skin lesions showed a definite tendency to heal in the course of time, leaving atrophic depigmented areas. In one of our cases a biopsy of one of these showed a typical sarcoid granuloma. These areas would become pigmented later with complete return to normal skin. Complete resolution of the skin lesions without any residual evidence occurred in 60 per cent of our cases with skin involvement.

Eye. Ocular lesions occur frequently as an accompaniment of sarcoidosis and occasionally may be the presenting manifestations. The incidence of this complication in recently reported larger series varies from 17.9 per cent to 44.0 per cent.[15,16] Nine of our patients (38 per cent) had ocular lesions. Sarcoidosis may affect almost any structure of the eye or its adnexa. Iritis or iridocyclitis is the most common form of eye involvement. Less commonly there may be nodules or calcareous lesions in the conjunctiva. Woods[16] states that it is doubtful if true sarcoid nodules occur primarily in the cornea although the cornea may be involved by degenerative changes secondary to uveitis. Optic neuritis, retinitis and chorioretinitis have been reported in isolated cases. The eye lesions noted in our cases were iritis, uveitis, secondary glaucoma, corneal opacities and chorioretinitis. The lesions in two patients resulted in bilateral blindness; another patient became blind in one eye and this later had to be enucleated because of painful secondary glaucoma. In some cases there was complete or nearly complete healing.

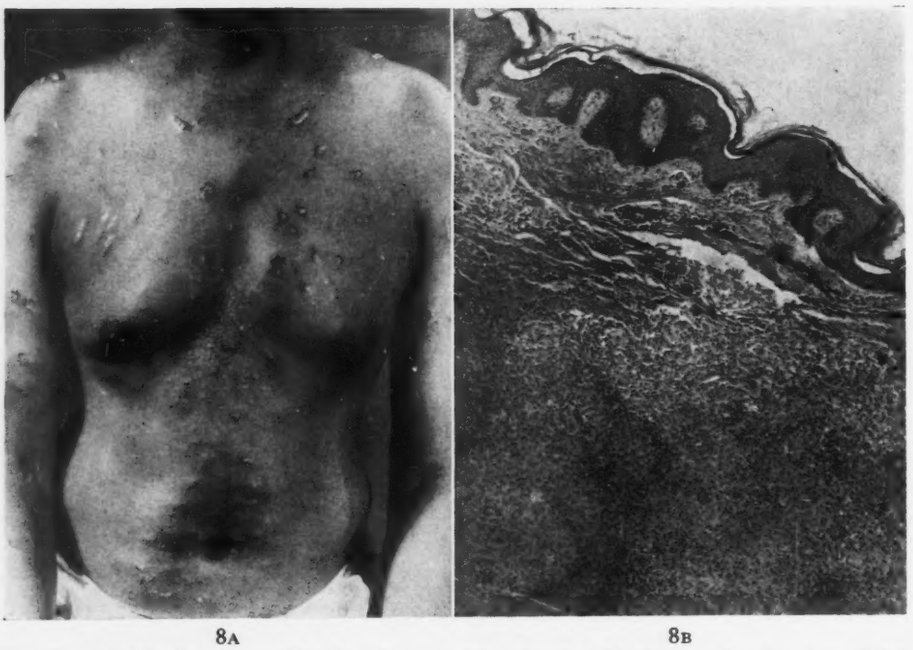

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FIG. 8. A, A fifty-four year old colored man with extensive skin lesions showing superficial ulceration. There are two biopsy scars over the clavicles. This patient also had subcutaneous granulomas of the Darier-Roussy type over the forearms; B, biopsy of a subcutaneous lesion showing a large subcutaneous granuloma only part of which is shown here; × 60.

Bones and Joints. Bone involvement is well known and has been reported in from 10 per cent to 25 per cent of several series of cases.[4,15,17] In our study bone involvement was found only in two cases (8 per cent) despite the fact that all patients had x-rays of the hands and feet, some of them many times. Two roentgenographic types of involvement are described: (1) circumscribed punched out areas of rarefaction without reactive changes and (2) a diffuse form with lattice-like appearance. Both of our patients showed the circumscribed punched out areas in the hands and feet without other involvement. While the bone lesions show a predilection for the hands and feet, other bones are occasionally involved.[18] A characteristic feature is the absence of significant pain due to the osseous lesions. The lesions may progress to mutilating deformity of the involved parts with the passage of time. Reisner[4] reported evidence of healing in a third of his cases and states that regression was more apt to occur in the diffuse form than in the circumscribed type. Our observations were too limited to permit us to draw any conclusions. It must always be remembered that a negative finding on x-ray does not necessarily mean absence of pathologic change, for it is well known that lesions may be found even in the absence of demonstrable x-ray findings.

Joint manifestations are not generally attributed to sarcoidosis. Review of the literature reveals individual cases with arthritis or joint pain during the course of the illness but little emphasis has been placed on this association. An exception is the report by Castellanos and Galan[19] of a six year old boy with arthritis resembling Still's disease occurring during the course of sarcoidosis. Although biopsy of the synovial membrane did not disclose typical sarcoid granulomas, they believed that the two were related. Burman and Mayer[20] had previously reported an eight year old child with a similar picture in which sarcoid granulomas were found in the synovia. Riley[5] stated that five of his patients were considered to have rheumatic fever with or without cardiac involvement. We are inclined to agree with Castellanos and Galan and believe that the joint symptoms and sarcoidosis are related. Six of our patients (25 per cent) had joint pain frequently accompanied with swelling and heat. The response to salicylates was never dramatic and frequently was lacking. Two patients were previously diagnosed as having rheumatic fever. The rheumatic manifestations included muscular

pain in some of our patients. The joint involvement was always multiple and occasionally there was migratory polyarthritis resembling that of rheumatic fever. The joints did not show marked swelling although on occasion there was evidence of slight effusion. It is our impression that these patients did not have rheumatic fever but rather a syndrome resembling rheumatic fever. We wish to emphasize the fact that sarcoidosis should be considered whenever one meets atypical rheumatic fever, especially in the Negro. An illustrative case report follows:

CASE IV. A thirty year old colored male was admitted to the hospital complaining of fever and soreness of the chest muscles of four weeks' duration. Several days after the onset of his illness he noted pain in the right arm with subsequent localization of the pain to the right elbow. Pain subsequently migrated to the legs and ankle joints. He consulted his physician who made a diagnosis of rheumatism. On the day of admission the left ankle became hot, swollen and tender. Past history included frequent nosebleeds but was otherwise irrelevant.

The patient was febrile and acutely ill. The heart and lungs were normal. Liver and spleen were not palpable. Motion of the shoulders, elbows, knees and ankles was painful. The left ankle was swollen, hot and tender. There was no lymph node enlargement.

Routine blood count and urine examination were normal. Sedimentation rate (Wintrobe) was 38 mm. per hour. Two studies for agglutinins for specific fevers were negative. Two blood cultures were sterile. Three cultures of gastric washings showed no acid-fast bacilli. Electrocardiogram was within normal limits. Chest x-ray showed increased density in both hilar regions. X-rays of the hands and feet were normal.

The patient's temperature on admission was 103.8°F. and for the first five days there was daily elevation of temperature to between 100° and 104°, after which it gradually subsided. The first impression was that the patient had rheumatic fever. However, chest x-ray showed some increased density in both hilar regions and sarcoidosis was suspected. Tuberculin reaction with PPD No. 1 was positive. Gastric washings were negative on culture for acid-fast bacilli. The axillary lymph nodes became palpable three weeks after admission. Biopsy of one of these confirmed the diagnosis of Boeck's sarcoid. The patient has been followed up for two years with gradual decrease in the hilar adenopathy that developed between six months and one year after the onset of his illness.

Spleen. Enlargement of the spleen has been found in 24 per cent of a series of cases of sarcoidosis collected from the recent literature. The degree of enlargement has been variable, from spleens barely palpable to massive splenomegaly. In a case seen by one of us (B. R. G.) the clinical picture was that of Banti's syndrome with leukopenia, anemia and hemorrhage from esophageal varices. The spleen showed the typical picture of sarcoid granulomas. Cases have been reported of splenomegaly and secondary thrombocytopenic purpura.[21] There has also been a report of spontaneous rupture of a sarcoid spleen.[22] The incidence of splenomegaly in our series was very much lower than in the experience of others. Only two patients (8 per cent) had splenomegaly. One patient had a palpable spleen when first seen in October, 1947, two years after the onset of his illness. The spleen remained palpable until May, 1948, but was no longer palpable when the patient was seen five months later in October, 1948. There was general improvement in his clinical picture. Of our three autopsied cases only one had splenomegaly. We have no explanation for the unusually low incidence in our series of cases.

Liver. Enlargement of the liver occurs with about the same frequency as splenomegaly in sarcoidosis. An analysis of 136 cases (112 from the literature plus our twenty-four) shows that the liver was palpable in 23 per cent of cases. In our study only three patients (13 per cent) had palpable livers. Abnormalities in liver function tests have been reported but we made no special study of this point. Of considerable importance is the frequency with which granulomas can be demonstrated in liver tissue obtained by needle biopsy. Klatskin and Yesner[23] report that positive biopsy evidence was obtained in 75 per cent of their cases and this is consistent with earlier reports in the literature. It is noteworthy that the granulomas may be demonstrated in the absence of hepatomegaly. These observations are of considerable importance when no accessible lymph nodes are available for biopsy.

Heart. The heart may be involved in two ways. There may be direct involvement with sarcoid lesions, a sarcoid myocarditis. This may manifest itself in sudden death which may occur without previous history of cardiac difficulty.

In other cases the clinical picture is that of congestive failure which is progressive and refractory despite therapy directed toward the heart. The cardiac involvement may be indirect as a result of extensive pulmonary pathology leading to a cor pulmonale. Involvement of the heart may be manifested in the electrocardiogram by arrhythmias, conduction defect, paroxysms of tachycardia or right ventricular enlargement. Three of our patients had cor pulmonale and all died.

Twenty-three of our patients had electrocardiographic study on at least one occasion. Four patients showed the pattern of right ventricular enlargement. Three of these were our fatal cases. The other gave a rheumatic history but had no definite evidence of heart disease. One patient, during his acute active stage, had a bigeminal rhythm on one occasion.

Nervous System. Involvement of the nervous system is not generally considered to be a prominent feature of sarcoidosis. Consequently it was surprising to find that seven of our cases (29 per cent) showed involvement of the nervous system. The disease may involve any part of the nervous system.[24] The structures most commonly involved are the facial nerves with resultant Bell's palsy. This may occur with or without concomitant parotid involvement. Involvement is usually unilateral although it may be bilateral. The condition resolves within several weeks in most instances although occasionally the paralysis may be persistent. Three of our patients showed unilateral Bell's palsy. In one case the paralysis was still present nine months after the onset. There may also be difficulty in swallowing, paralysis of the vocal cords or loss of taste. One of our patients had a transient impairment of taste which improved over a period of several months. Nerve deafness and paralysis of the extra-ocular muscles have been noted but did not appear in our series. There may be involvement of the peripheral nerves with paresthesias, pain and reflex changes. Meningeal and cord lesions have been noted. One of our patients (Case 1) showed a bizarre neurologic picture due to cord involvement. Another patient had herpes zoster during the active stage of his sarcoidosis. Although no histologic confirmation could be obtained, we assumed that the lesion was due to involvement of the ganglia very much as occurs in Hodgkin's disease and the leukemias. Hypothalamic or pituitary involvement may result in diabetes insipidus.[25] This was present in one of our cases. No histologic confirmation of the diagnosis was obtained in this case but the clinical course was so typical of sarcoidosis that his case was included in the series. It is apparent that the diagnosis of sarcoidosis should be considered in obscure conditions of the nervous system.

Miscellaneous. The widespread distribution of the lesions results in manifestations in practically every organ in the body. The *parotid gland* is involved often, usually with concomitant paralysis of the facial nerve. During this time there is fever. When there is associated uveitis, the clinical picture of parotid and eye disease is called *uveoparotid fever* or *Heerfordt's syndrome.* Three patients in this series showed this syndrome with concomitant Bell's palsy as noted before. At times the parotid may be involved with accompanying lacrimal and sometimes submaxillary gland involvement, giving rise to the clinical picture of *Mikulicz's syndrome.* None of the patients in this series showed a Mikulicz's syndrome but one of us (B. R. G.) has previously observed a patient with this syndrome due to sarcoidosis. Spontaneous regression of the parotid swelling is the rule and occurred in all three cases within several weeks to several months of the onset.

Sarcoidosis may be accompanied with *fever,* especially as part of the syndrome of uveoparotid fever. Low grade fever also occurs during the active stage of sarcoidosis and may last for weeks or months. Occasionally fever may be the most prominent clinical feature and there may be a septic febrile course. We have already called attention to the fever associated with the clinical picture of atypical rheumatic fever. One of our patients had fever over a period of more than six months. Neither penicillin nor streptomycin had any effect on the fever.

Involvement of the *tonsils* has been stressed by Schaumann as part of the generalized disease of the lymphatic system. He found evidence of sarcoid lesions in each of twenty-one active cases.[26] Gravesen[27] noted involvement in forty-five of seventy cases. The tonsils may show no visible abnormality yet microscopic examination may show the lesions. It is of importance to remember that in patients without accessible lymph nodes tonsillectomy may make possible a definitive diagnosis. Unfortunately in many of our cases the tonsils had been removed previously. The *kidney* has shown scattered lesions at

autopsy, but clinical evidence of renal involvement was lacking in our cases. Albuminuria and azotemia have been reported by others.

LABORATORY DATA

Blood Picture. There is no specific or characteristic blood picture for sarcoidosis and in most cases this is normal. The subject of the variations in blood picture has recently been reviewed by Bruschi and Howe.[21] Four of our twenty-four patients had red cell counts lower than 4.0 million. Three patients, after periods from one to three years, had a return of the red count to normal. The other patient died with persistence of his anemia. Hemolytic anemia has been noted in cases with splenomegaly[28] but this was not seen in our series. Rarely polycythemia may occur, particularly in the presence of marked pulmonary involvement with cor pulmonale. The leukocyte count is usually normal although there is a tendency for leukopenia to occur. Four of our patients had a leukocyte count of less than 4,000 at some time during observation. None of these patients had splenomegaly. Only one patient had a leukocytosis with white cell counts varying from 12 to 15 thousand over a period of three years. Eosinophilia has been reported and occurred occasionally in our series. It was always difficult to evaluate the role of concomitant intestinal parasites and drug therapy, notably streptomycin. However, some cases showed slight eosinophilia without concomitant parasites or drug therapy. Monocytosis above 12 per cent was found in four of our cases. Platelet counts were within normal limits in all of our patients although thrombocytopenia and even pancytopenia have been reported.[21]

Bone Marrow Aspiration. Sternal marrow aspirations were performed on eighteen of our patients and direct smears made on slides were stained with Wright's stain and counterstained with Giemsa's stain. No specific lesion was found. The marrow of most patients was normal in cellularity and in the distribution of cells. Some patients had a varying degree of non-specific hyperplasia of the granulocytic or erythrocytic series of cells. An occasional patient had a slight increase in plasma cells. Cultures of the marrow in three cases were negative for acid-fast bacilli. Lucia and Aggeler[29] also found no granulomas and noted only a mild granulocytic stimulation. Sarcoid granulomas have been demonstrated by others.[30] Gormsen[31] demonstrated granulomas in marrow sections from some patients with sarcoidosis. Unfortunately we did not attempt a systematic study of sections of aspirated marrow but it is possible that this type of study might be more productive than smears of the marrow. In the few cases in which this was done no granulomas were seen. It is likely that smearing of the marrow disrupts any granuloma which might have been present.

Blood Proteins. The total proteins of the blood are frequently increased, and often the globulins are increased even though the figure for total protein is within the normal limit. In our patients a total blood protein level of 8.0 gm. or more was considered elevated and eight of our cases (33 per cent) showed elevation. The highest level for blood proteins encountered in this series of cases was 8.8 gm. per cent. An arbitrary level for the upper limit of normal for globulin based on experience in our own laboratory was selected. Because of difference in technic instituted in 1948, a level of 3.0 gm. or more before that time and 3.7 gm. or more since 1948 was taken as the upper limit. Sixteen cases (67 per cent) showed hyperglobulinemia. The protein levels tended to return to normal as the disease showed tendency toward improvement. In two of the fatal cases in whom repeated estimations of the blood proteins were made, it was noted that the globulin level progressively increased until the patient's death. In the other patient only one total protein determination was made because the patient died about a month after admission to the hospital.

Serum Calcium. Elevation of the serum calcium level has been reported in sarcoidosis. Twenty-two of our patients had at least one determination of serum calcium; nine of these patients had levels over 11.0 mg. per cent. Most of these elevated values were only slightly above normal, the highest value being 13.5 mg. per cent. There was no correlation between elevation of the serum calcium and the protein level or bone changes demonstrable on x-ray. In fact, both patients with bone changes had normal calcium levels.

SKIN TESTS

Tuberculin Reaction. A negative reaction to tuberculin is considered an important finding in sarcoidosis. The results in most instances are that 60 per cent to 80 per cent of the cases show negative reactions to tuberculin. We used purified protein derivative for routine testing of patients, and skin tests were repeated on re-

admission to the hospital. Fifteen patients (63 per cent) were negative to PPD No. 1 and No. 2. Table 1 shows the comparative incidence in several recent reports.

Histoplasmin and Coccidioidin Skin Tests. Nineteen of our patients had skin tests performed

TABLE 1

INCIDENCE OF NEGATIVE TUBERCULIN REACTIONS IN SARCOIDOSIS

Author	No. of Cases	Negative Tuberculin Tests	Negative Tuberculin Tests (%)
Moyer & Ackerman[15]	28	11	40
Reisner[4]	35	21	60
Riley[5]	51	33	65
McCort et al.[14]	25	21	84
Authors' series	24	15	63
Total	163	101	62

with histoplasmin and coccidioidin antigens. All of the patients had negative coccidioidin reactions; one patient had a positive histoplasmin reaction. There was nothing in the clinical course in this case to suggest histoplasmosis.

Kveim Reaction. Recent interest has been stimulated by a skin test for sarcoidosis introduced by Kveim. A study of this subject has been made by Nelson[32] who found that the test was positive in about 75 per cent of active cases. It was uniformly negative in healed or inactive sarcoidosis. The antigen used is obtained from lymph nodes of patients with sarcoidosis and prepared as a 10 per cent suspension in normal saline. A positive response is a papular lesion requiring weeks to develop and lasting for several months. The test is generally negative in other conditions. An interesting observation is that antigen prepared from normal human spleen, saline suspension of leukemic human lymph nodes or killed tubercle bacilli may also give a positive Kveim reaction in patients with sarcoidosis. We have had no personal experience with this test.

DIAGNOSIS

The diagnosis of sarcoidosis may be suggested by any of a variety of clinical manifestations, by x-ray findings in the chest or bones, or by hyperglobulinemia or hyperproteinemia. In the usual case the problem is not difficult and biopsy of an accessible peripheral lymph node will confirm the diagnosis. A single negative lymph node biopsy does not rule out sarcoidosis and occasionally it is necessary to remove another node in order to substantiate the diagnosis. The problem becomes more difficult when there are no available peripheral lymph nodes or skin lesions. If one can wait, the lymph nodes may enlarge later, as in Case IV, and biopsy may be performed. However, it may not be expedient to wait and a problem presents itself of how to establish the diagnosis on a histologic basis under such circumstances. There are several possibilities which may prove productive. Liver biopsy may show granulomas; however, these are not specific for sarcoidosis but may also occur in a variety of other diseases such as tuberculosis, brucellosis, tularemia, syphilis and a number of other conditions.[23] The clinical picture in many of these conditions may aid in differentiation from sarcoidosis. Another possibility is the operative removal of some of the areolar tissue from back of the clavicle or upper mediastinum through a small incision in the neck. Sarcoid lesions have been demonstrated in small nodes in such tissue. If the tonsils are present sarcoid granulomas may be demonstrated in them, as shown by Schaumann.[26] In two of our patients with massive mediastinal nodes thoracotomy and biopsy was performed when the diagnosis could not otherwise be made. Lastly, bone marrow aspiration may be of value. If the marrow is permitted to clot and this material sectioned as tissue, granulomas may be seen. Our own experience has been primarily with bone marrow smears and these have been of no value. In the few instances in which we have made sections of clot, granulomas were not found.

PROGNOSIS

Sarcoidosis is a chronic disease which runs a prolonged course over a period of years. Many observers, impressed with the remarkable contrast between the extent of involvement of various organs on the one hand and the apparent good general health of the patient on the other, have stated that the disease is benign. The recent reports of Reisner[4] and Riley[5] cast doubt on the belief that the disease has so good a prognosis. Reisner reported a mortality of 25 per cent of his patients with adequate follow-up. Five of his

seven deaths were due to superimposed tuberculosis. Three of his patients developed blindness; in two cases this was total and in the other there was blindness of one eye. Riley reported ten deaths in his series, a mortality of about 20 per cent. He also found that five of his patients developed irreversible pulmonary changes and seven, active tuberculosis. In five of his twelve patients with involvement of the uveal tract the disease progressed to blindness. We wish to emphasize, on the basis of our observations, the uncertainty of the prognosis. Three of our patients died as a direct result of their disease, a mortality of 13 per cent. Three of our patients have blindness as a result of sarcoidosis, two bilateral, one unilateral. Our patient with unilateral blindness also has a severe diabetes insipidus presumably due to involvement of the hypothalamico-hypophyseal system. However, some patients over a period of years may show complete remission without residual findings. Reisner noted that nine of twenty-eight cases (31 per cent) adequately followed up showed complete regression. Riley reported complete regression in 13 per cent of his cases and the disease was improving in some other patients. Three of our twenty-four patients (13 per cent) had complete regression during the course of observation. Three others had complete clinical regression although hyperglobulinemia persisted and further observation of these patients will be necessary. The patient with diabetes insipidus had no other residual manifestations of sarcoidosis and it is possible that permanent scarring was present to account for the diabetes insipidus.

TREATMENT

There is no specific treatment available at the present time. The tendency of the disease to show spontaneous regression makes evaluation of any therapeutic measure most difficult. Many forms of treatment have been advised but none has been proven by the test of time. A number of measures have been used in this series. Streptomycin was used in six cases with courses of treatment lasting from twenty-one to 120 days. No demonstrable effect could be attributed to the drug. In one patient hilar and mediastinal lymph node enlargement progressed despite streptomycin. Aureomycin was used in one case without any significant effect. Following the work of Snider,[33] nitrogen mustard was used in six cases. There was no clear-cut evidence of improvement in any patient. In fact, one patient developed skin lesions shortly after completing a course of nitrogen mustard. Calciferol was used in only one case. This patient developed hypercalcemia (serum calcium 18.0 mg. per cent) and hypercalcinuria which required discontinuance of therapy. The skin lesions became worse during treatment with this drug. Three patients received roentgen-ray irradiation without any effect. Some authors believe that radiation may be beneficial although Donlan[34] found that radiation did not benefit any of eleven patients with sarcoidosis. ACTH and cortisone eyedrops were used in one case without effect on the pulmonary lesions although the eye lesions seemed to respond slowly. It cannot be said that the improvement was due to the treatment. Recently, Sones and his co-workers[35] have reported beneficial effect of parenterally administered cortisone in two cases of sarcoidosis.

SUMMARY

This report analyzes twenty-four cases of sarcoidosis observed over a period of nearly five years. The disease is no longer to be considered rare. It is more common in the Negro than in the white patient and is manifested by a variety of clinical expressions. Most common involvement is of the lungs and lymph nodes although the eyes, skin, bones, liver and spleen are frequently affected. Our studies emphasize the occurrence of rheumatic complaints and nervous system involvement. The prognosis is not as benign as has been thought generally. Three of our patients died as a direct result of their disease. No form of treatment has proven of consistent value.

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Seminars on Congenital Heart Disease

Angiocardiography in Congenital Heart Disease*

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ENCASED in glass and labeled "an antiquated instrument," a stethoscope has been on display for several years in the office of an eminent American radiologist. That this example of academic isolationism constitutes a purely facetious gesture is evidenced by the unusual clinical acumen of the radiologist in question. All too often, however, the problem of diagnosis in congenital heart disease is attacked by independently acting and thinking individuals, each stressing a particular method of investigation to the exclusion of others. Although cardiac catheterization and angiocardiography constitute effective diagnostic technics, neither is invariably sufficient or always indicated. A general understanding of all phases of congenital heart disease should be a prerequisite to diagnostic participation in any capacity. Radiologists must not scorn the stethoscope, pediatricians should not regard angiocardiography as a lethal procedure to be avoided at all costs and those engaged in catheterization should recognize their own diagnostic inadequacies in certain situations.

Angiocardiography is to the cardiovascular system what barium study is to the gastrointestinal tract. The method, first described in 1938,[1] consists of the radiographic study of the thoracic cardiovascular structures during their opacification by a radiopaque fluid rapidly injected into a peripheral vein. Since in the normal but a short time (usually less than ten seconds) is required for the opaque medium to complete its passage through the chambers of the heart, the pulmonary circulation and the aorta, modern technic requires that rapid serial radiography be employed.[2,3] For the angiocardiographic study of congenital cardiac malformations, exposure rates of two per second are highly desirable and may be obtained with commercially available apparatus.[4–7]

Since at least twenty-six deaths are known to have followed angiocardiography[8] and since the hazard of the procedure appears to be highest in young patients with congenital heart disease, care should be exercised in the selection of cases for examination. Academic interest alone is not an indication. It is our belief that all patients with cyanotic congenital heart disease should be studied angiocardiographically *if surgery is planned.*[9] Even in those centers where experience in the diagnosis and treatment of such malformations is at its most advanced state mistakes in diagnosis are not infrequently encountered at operation or autopsy.[10] It is occasionally difficult for the pathologist to identify with certainty the nature of a complex malformation at autopsy and it is manifest that the problems of the surgeon, limited to brief inspection of the outside of a rapidly moving heart, are proportionately greater. In the typical case of tetralogy of Fallot it is of great value to the surgeon to be able to study the anatomy of the brachiocephalic and pulmonary arteries to be anastomosed. Finally, angiocardiography may facilitate selection of the proper side of the chest to be entered.

NON-CYANOTIC CONGENITAL HEART DISEASE

Angiocardiography, although frequently employed, is rarely necessary or indicated in the study of a variety of non-cyanotic congenital cardiac lesions, chief among which are patent ductus arteriosus and isolated septal defects. Here clinical examination and cardiac catheterization are in general sufficient and often more reliable than contrast visualization. In the presence of shunting of blood from the left or arterial

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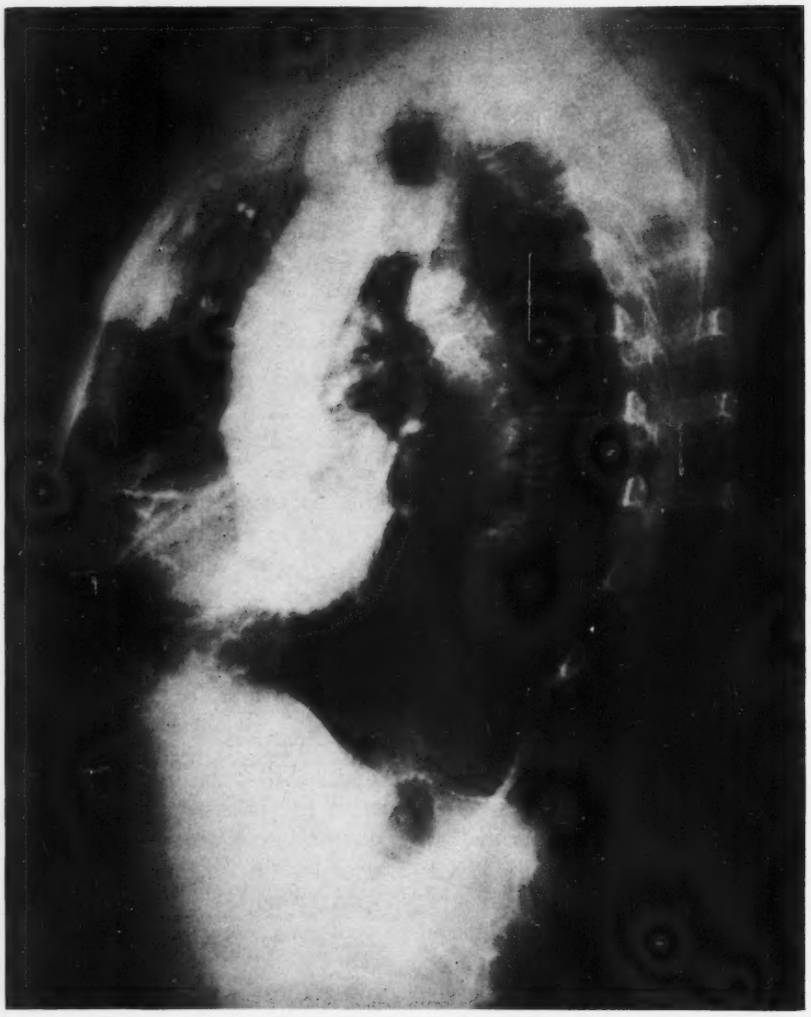


FIG. 1. *Coarctation of the aorta:* A forty year old woman (N.Y.H. 605 364) had hypertension since childhood and headaches recently. Blood pressure was 200/100 in arms; unobtainable in legs. Rib notching and left ventricular enlargement were present. Angiocardiography (left oblique projection, 9 seconds after the beginning of the injection) shows a dilated ascending aorta and brachiocephalic branches. Actual coarctation is 2 cm. distal to the site of origin of the left subclavian artery. Mild post-stenotic dilatation of the descending aorta is present.

side of the heart to the right heart or pulmonary artery the contrast agent is diluted with arterial blood with the result that visualization is impaired. Recirculation of contrast agent from the left to the right side of the heart is difficult to identify with certainty when present and may be simulated because of technical factors in the absence of a defect. Despite the general unreliability of contrast visualization in such situations, the angiocardiographic findings are summarized hereafter for the sake of completeness and since the method occasionally proves to be of value in doubtful or atypical cases. There are several non-cyanotic congenital cardiovascular anomalies in the study of which angiocardiography plays an essential role. Coarctation of the aorta is the most important of these.

Coarctation of the Aorta and Other Aortic Arch Anomalies. The great majority of patients with coarctation of the aorta have a sharply localized area of aortic narrowing a short distance distal to the site of origin of the left subclavian artery. As a result upper extremity hypertension, lower extremity hypotension and abundant collateral arterial channels occur. The lesion is readily detected clinically. Atypical coarctation occurring in the descending thoracic aorta or in the upper abdominal aorta cannot

be differentiated from the usual lesion by clinical means, however, and is frequently of a diffuse rather than a localized variety.[11] Coarctation now constitutes an indication for surgery and angiocardiography is the most important preoperative examination.[12–16] It provides the surgeon with precise anatomic information concerning the lesion he is to attack, thereby allowing him to plan the procedure in advance and gauge the necessity for vascular grafting. It should not be necessary to resort to aortography[17–19] (direct or retrograde instillation of radiopaque fluids into the aorta), for properly conducted angiocardiography is easier to perform, less hazardous and adequately informative.

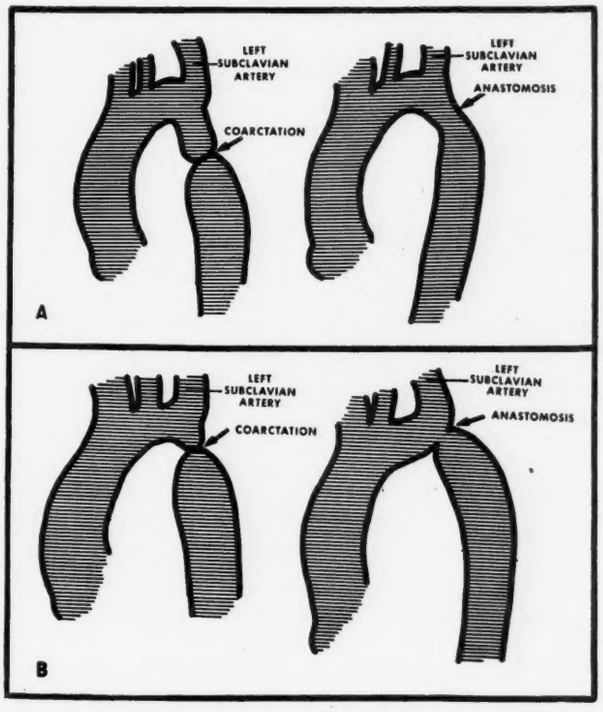


FIG. 2. *Coarctation of the aorta before and after surgery:* Tracings of angiocardiograms. A, before and after resection and anastomosis in a fifteen year old male. B, in this twenty-seven year old female shortness of the stub between the left subclavian artery and the site of coarctation made the operative procedure more difficult and resulted in slight compromise in the caliber of the anastomosis.

The projection of choice for the angiocardiographic study of coarctation of the aorta is the left anterior oblique, which provides an "open" view of the aortic arch in approximately the same plane as will be the surgical exposure. The characteristic findings in a case of coarctation are shown in Figure 1. In the rare instances of coarctation of the aortic arch proximal to the left subclavian artery or in cases of complete interruption of the aorta with blood flow to the lower extremities through a patent ductus arteriosus, angiocardiography can be expected to reveal the abnormal anatomy satisfactorily.[9] These lesions can also be accurately identified by clinical means if careful attention is paid to blood pressures in all extremities, carotid pulsations and the presence and localization of cyanosis.[20] Angiocardiography is also of certain practical value and considerable academic interest in assessing the results of surgical procedures for coarctation of the aorta. (Fig. 2.)

An anomalous course of the aorta wherein the distal portion of the arch is kinked at the usual site of coarctation has been observed by us[9] five times and has been described by others.[16,21] In this lesion there is no anatomic or physiologic narrowing of the aorta and neither symptoms nor hypertension develops. As in some instances of coarctation, the appearance of the aorta in the left anterior oblique projection suggests that a short ductus arteriosus or ligamentum arteriosum has exerted traction upon the aorta. (Fig. 3.) The lesion can usually be identified on the basis

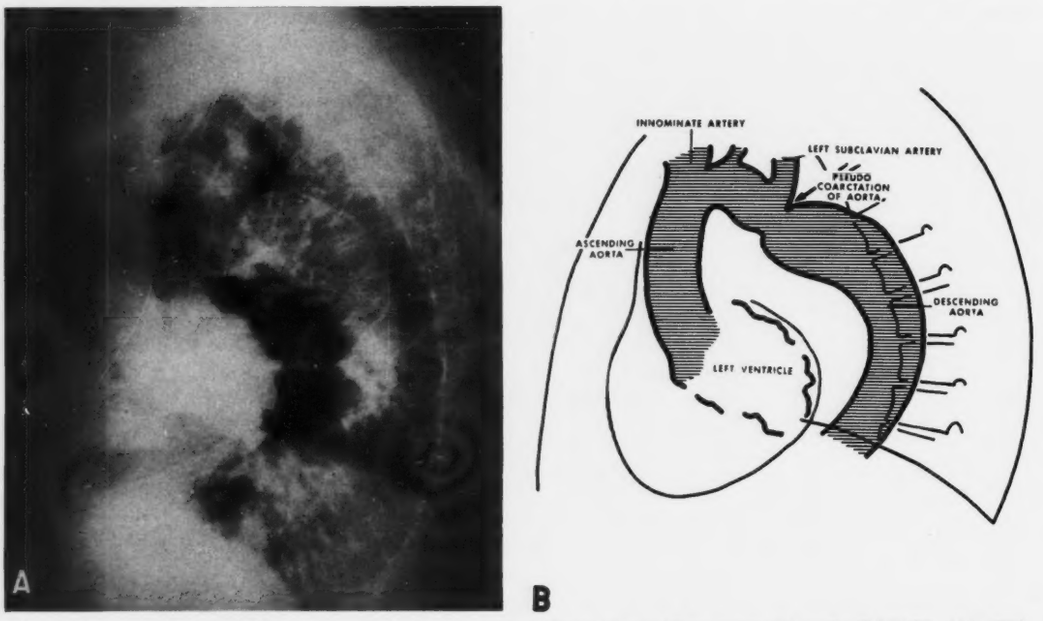


FIG. 3. *Aortic arch anomaly (pseudocoarctation):* An asymptomatic forty-four year old male (N.Y.H. 601 670) was referred for angiocardiography after a routine chest film was interpreted as showing a mediastinal tumor. There was no discrepancy between arm and leg blood pressures and no murmur was present. A, angiocardiogram (lateral projection at 9 seconds) shows an anomaly of the aortic arch similar in appearance to coarctation of the aorta. No physiologic constriction was present. B, tracing of A.

of conventional roentgenograms in the frontal projection. These reveal a double contour of the aortic knob. The lower, more medial prominence is of greatly increased density as compared to the upper and is quite round in shape, representing the end-on shadow of the horizontal segment of the aorta distal to the site of angulation.

Right aortic arch and "ring" anomalies of the aorta and its branches can usually be diagnosed accurately by conventional roentgenography[22] including study of the barium-filled esophagus. A common form of "ring" anomaly is that in which a right subclavian artery takes origin from the descending aorta, passing obliquely upward and to the right, posterior to the esophagus. In certain complex abnormalities angiocardiography has been of value.[22,24] Views are best made in two projections at right angles to each other.

Interatrial Septal Defect. Since pressure within the left atrium normally exceeds that in the right, blood is predominantly shunted from left to right through isolated defects in the atrial septum. Actually a small quantity of blood also passes in the opposite direction during certain phases of the cardiac cycle.[25,26] The left to right flow of blood may attain very large volumes, often exceeding the systemic flow; and since this blood is propelled in circles by the right ventricle, the latter chamber becomes greatly enlarged. Due to increased blood flow and pressure within the lesser circulation the pulmonary arteries become markedly enlarged and pulsate forcefully ("hilar dance"). The demonstration of right ventricular and atrial enlargement, engorgement and increased pulsation of the pulmonary arteries by fluoroscopy plus the presence of the characteristic systolic murmur usually suffices to establish the diagnosis.[27] Cardiac catheterization is the confirmatory procedure of choice and usually there is little reason to perform angiocardiography.

The angiocardiogram in interatrial septal defect reveals right heart and pulmonary arterial enlargement. In our experience contrast agent cannot be recognized to pass from the left to the right atrium unless associated defects such as pulmonary stenosis or tricuspid atresia are present. The usual finding is that of persistent opacification of the right atrium, the right ventricle and the pulmonary arteries which lasts during the entire period of cardiac filling and results from recirculation of opacified blood from the left to the right atrium. (Fig. 4.) Opacification of the chambers of the left heart and the aorta is usually of poor quality due to dilution of the contrast agent by large volumes of shunted blood.[28] Persistent opacification of

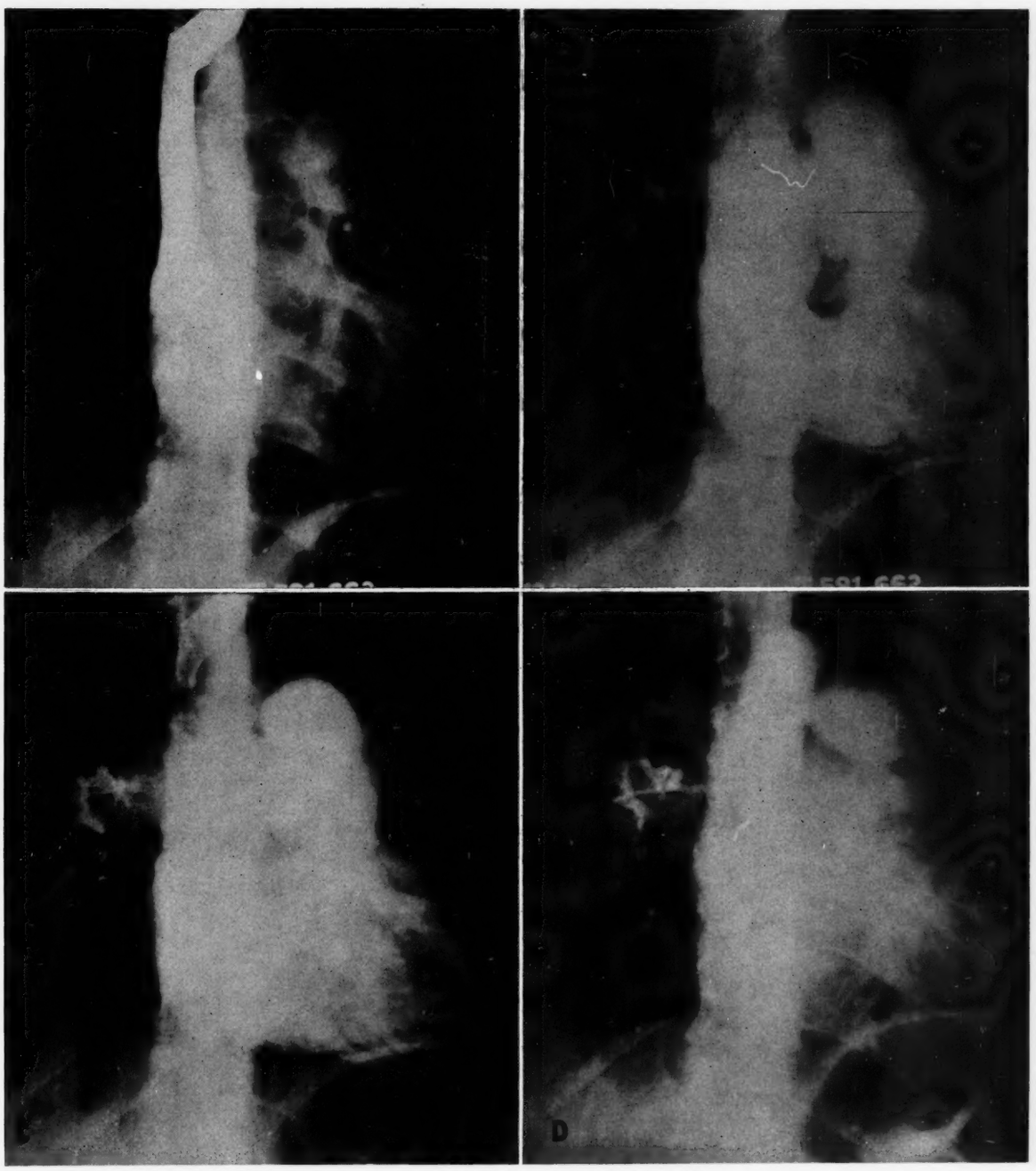


FIG. 4. *Interatrial septal defect:* A twenty-nine year old woman (N.Y.H. 596 662) with heart murmur since childhood. Dyspnea and fatigue one year. Loud diastolic and faint systolic murmurs heard at third left interspace. Fluoroscopy revealed dilated, vigorously pulsating pulmonary arteries. Angiocardiography in frontal projection. A, 1.0 second film shows Urokon sodium (70 per cent) entering superior vena cava and right atrium. B, at 2.5 seconds there is opacification of an enlarged right ventricle and dilated pulmonary arteries. C, at 3.5 seconds the right ventricular enlargement is strikingly shown. D, at 8.0 seconds the left atrium and ascending aorta are well visualized while right heart chambers and pulmonary vessels still contain contrast substance, indicating the probable presence of an interatrial septal defect.

the pulmonary arteries also occurs as a result of large interventricular septal defects, patent ductus arteriosus and defects in the aorticopulmonary septum,[9] but the right atrium does not share in the opacification. It is occasionally difficult to establish with certainty that such recirculation of contrast agent is actually present. A slow injection or the trapping of contrast agent in arm or neck veins may result in prolonged filling of the right atrium and therefore lead to a mistaken angiocardiographic diagnosis of interatrial defect.[29]

Interventricular Septal Defect. Angiocardiography may show no abnormality in the presence of small defects in the ventricular septum. There may be evidence of reopacification of the right ventricle (but not the right atrium) at the time of left heart filling,[30] but as is the case with interatrial defects, the finding is difficult to evaluate. We have observed a high interventricular septal defect (established with reasonable certainty at cardiac catheterization) in which there was angiocardiographic demonstration of shunting of blood in both directions across the defect, pulmonary hypertension being present.[9] Even after cardiac catheterization it may be difficult to distinguish between such a lesion and the Eisenmenger complex.

Patent Ductus Arteriosus. In common with most lesions causing left to right shunting of blood angiocardiography leaves much to be desired in the study of patent ductus arteriosus. The angiocardiographic findings which have been observed[31–34] include: (1) dilation of pulmonary arteries; (2) high position of the left pulmonary artery; (3) persistent opacification of the pulmonary arteries at the time of aortic filling; (4) localized dilation of the aorta at the site of origin of the ductus; (5) a defect in the column of contrast substance within and at the time of filling of the left pulmonary artery caused by a jet of non-opacified blood issuing from the ductus; and (6) rarely, opacification of the ductus itself. These signs have all been absent in proved cases of patent ductus arteriosus. Thoracic aortography[17,18] reveals the anatomy of patent ductus arteriosus with clarity but its routine use is not justified since the diagnosis can usually be established by the stethoscope.

In rare cases of patent ductus arteriosus the pulmonary arterial blood pressure may be elevated to systemic levels. When this occurs the direction of flow across the ductus becomes reversed with the production of clinically and angiocardiographically typical findings.[35] As illustrated in Figure 5, early opacification occurs of the descending *but not the ascending* aorta while later films rule out the presence of stenosis of the aortic arch. As would be expected, this situation results in cyanosis localized to the lower but not the upper extremities.

Aortic Septal Defect. Since the two lesions produce the same hemodynamic abnormality, it is usually not possible by means of angiocardiography or cardiac catheterization to distinguish between patent ductus arteriosus and defects occurring between the aorta and the pulmonary artery just above the semilunar valves. Fortunately, the latter lesion is rare. The diagnosis may be suspected clinically and confirmed by thoracic aortography.[36,37] At least one such defect has been surgically repaired[38] although in general it must be considered an inoperable condition at present.

Uncomplicated Pulmonary Stenosis. Widespread use of cardiac catheterization is responsible for the increasing frequency with which the diagnosis of isolated stenosis of the pulmonary valve is made.[39] The finding of low pulmonary arterial and elevated right ventricular systolic pressures on cardiac catheterization constitutes a simple and convincing method for demonstrating pulmonary stenosis.[40] Attention is usually directed to the lesion by the finding of a systolic murmur in the pulmonary area and by x-ray evidence of an enlarged central pulmonary artery. In the absence of autopsy confirmation it is not possible to be certain that probe patency of the foramen ovale does not exist although a high right atrial pressure in the absence of cyanosis makes this complication most unlikely. If the foramen ovale is patent, the delayed onset of cyanosis may occur when, as a result of pulmonary stenosis, pressure in the right atrium rises to exceed that in the left atrium.

Angiocardiography in uncomplicated or isolated pulmonary stenosis usually reveals gross central dilation of the pulmonary arteries distal to the point of stenosis, the peripheral branches being normal or reduced in size.[32,41–43] The etiology of this poststenotic dilation remains obscure. The degree of dilation appears to be greater in older patients, suggesting that, acting over a long period of time, turbulent blood flow beyond the narrowed area may effect dilation of the vessel. In about half of the cases studied angiocardiography fails to reveal the actual

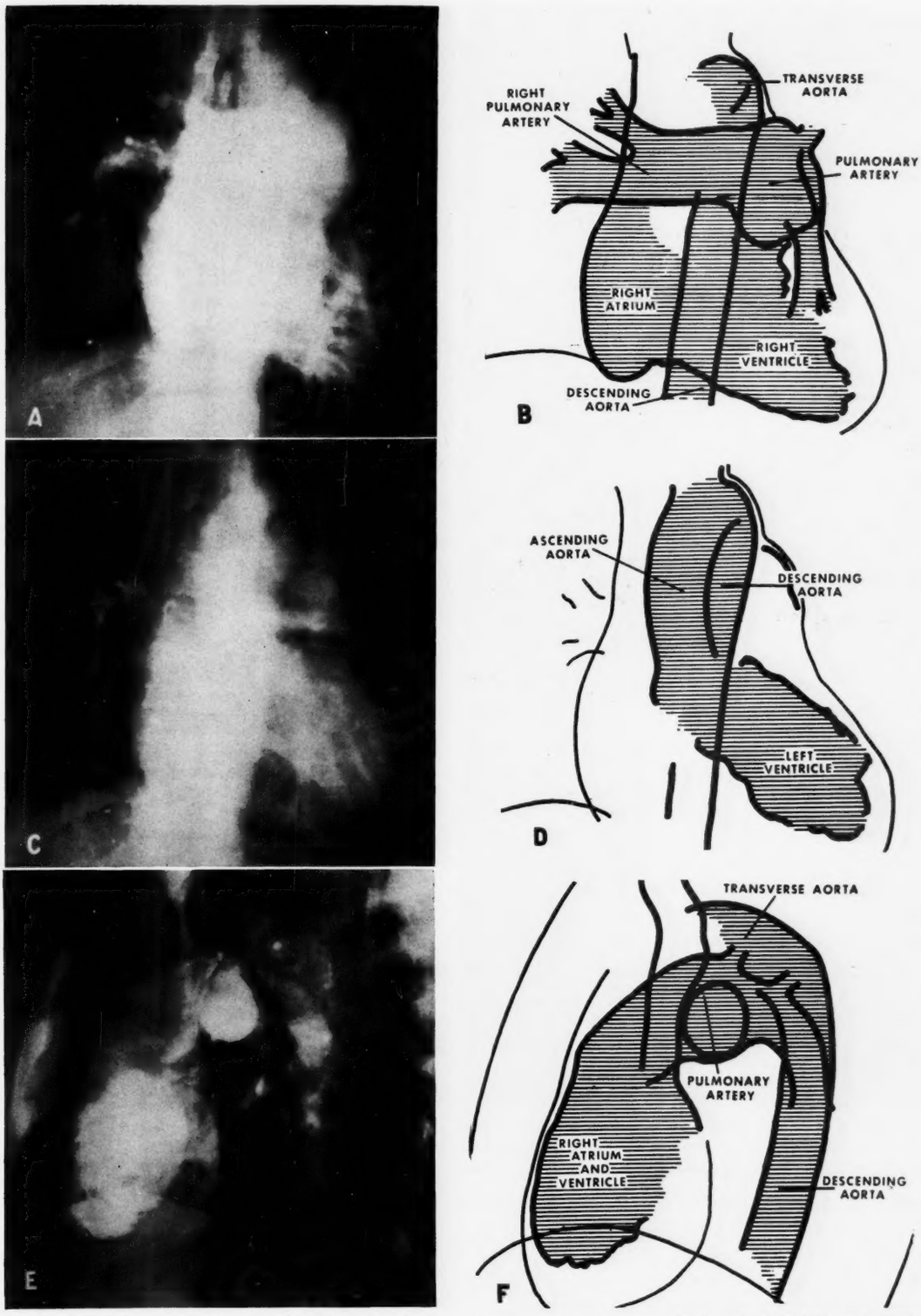


FIG. 5. *Patent ductus arteriosus, marked pulmonary hypertension:* A twenty-six year old female (N.Y.H. 501 693) known to have had a cardiac murmur since birth. Cyanosis was present in the toes but not in the fingernails. The peripheral blood pressures were normal. A, frontal angiocardiogram at 2.5 seconds. There is enlargement of the right ventricle and pulmonary arteries. The descending but not the ascending aorta is opacified, indicating passage of contrast substance from the pulmonary artery to the aorta. C, at 7.0 seconds the entire aorta is opacified. E, in lateral projection at 2.5 seconds, opacification of the descending but not the ascending aorta again occurs simultaneously with pulmonary arterial filling. Lesion confirmed at operation.

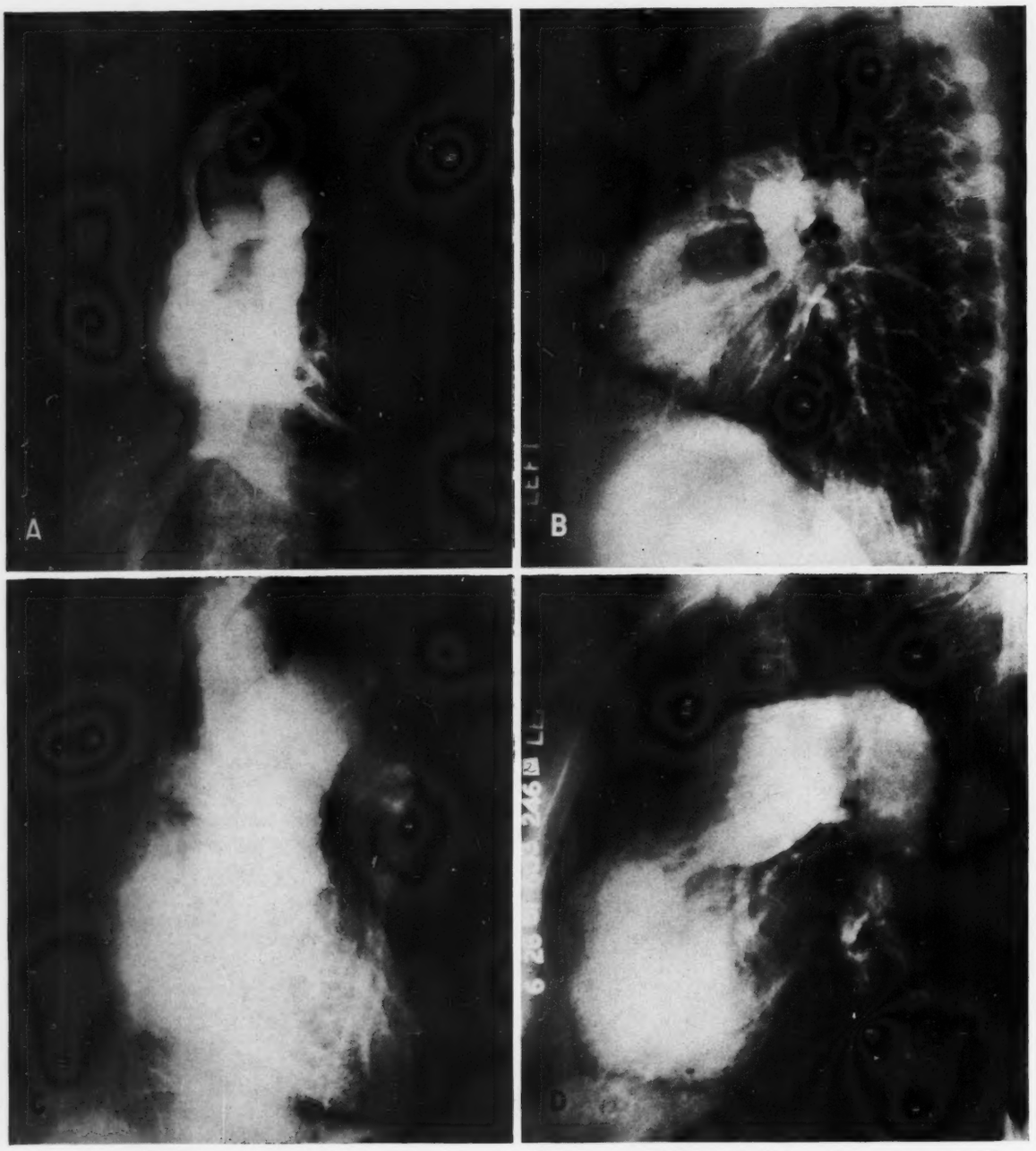


FIG. 6. *Pure pulmonary stenosis:* A and B show post-stenotic dilatation and deformity of the pulmonary arteries in a fifteen year old female. C and D reveal more marked dilatation in a thirty-seven year old female. There was no evidence indicating (or conclusively excluding) the presence of associated defect in either of these patients.

stenosis; however, by revealing the gross, usually irregular poststenotic enlargement, the method has added significantly to the diagnosis of pulmonary stenosis. (Fig. 6.) Cardiac catheterization is the definitive means of diagnosis during life and the only means of differentiating between this condition and congenital primary dilation of the pulmonary arteries.[44]

Anomalous Pulmonary and Mediastinal Veins. Drainage of all the pulmonary veins into the right atrium occurs rarely, must be associated with gross septal defects (usually between the atria) to be compatible with life and is always accompanied with cyanosis.[45] When the anomalous drainage is confined to all or part of only one lung, however, the condition is compatible with a long life free of signs or symptoms of disease. Unless its tip is manipulated into the

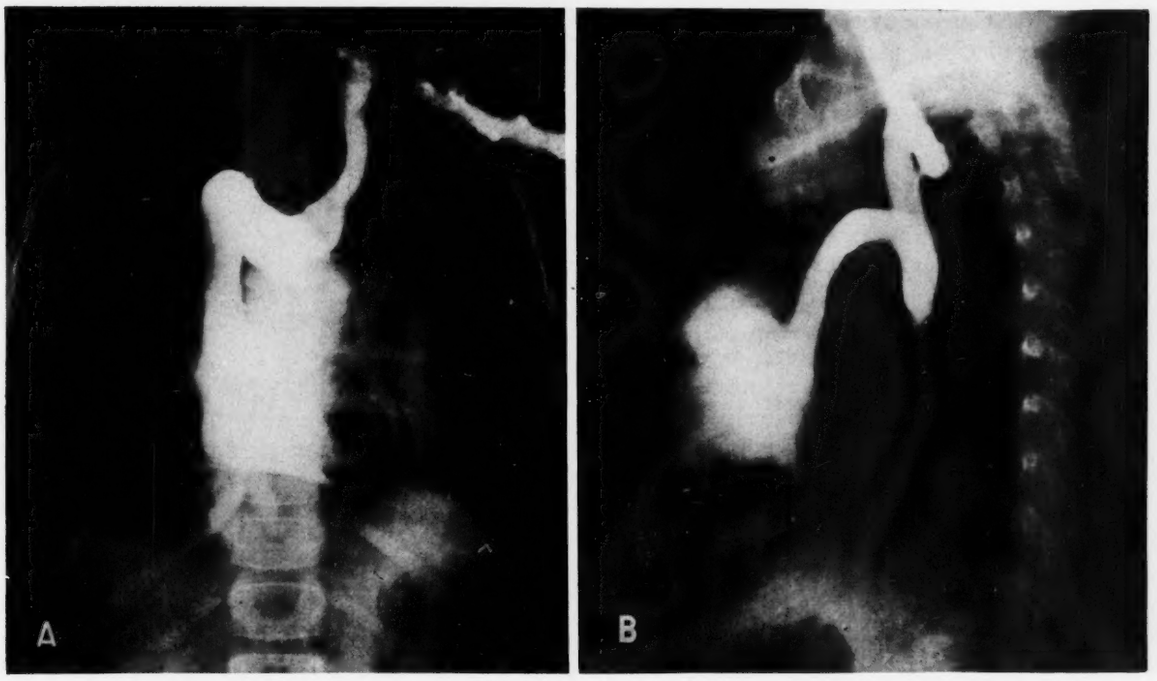


FIG. 7. *Anomalous mediastinal vein:* A seven year old girl (N.Y.H. 576 096). A pulsatile prominence was noted in the aortic knob area. A, frontal angiocardiogram at 1.0 second. B, lateral angiocardiogram at 1.0 second. An anomalous venous pathway from the left arm to the right atrium is seen. The left innominate vein passes beneath the aortic arch before curving upward and to the right, finally entering the normally positioned superior vena cava. From DOTTER, C. T. and STEINBERG, I. Angiocardiography. New York, 1951. Paul B. Hoeber, Inc.

anomalous vein, the cardiac catheter provides findings identical with those produced by an interatrial septal defect.[27] Angiocardiography (best performed in the frontal projection) can be relied upon to show the abnormal pulmonary vein and its site of drainage, leaving no doubt as to the diagnosis.[45–47] The physiologic consequences of such a lesion are interesting. On the angiocardiogram it is apparent that the pulmonary arteries to the abnormally drained lung are smaller than those to the normally drained side. As might be anticipated, the right heart chambers usually appear enlarged. In effect, a patient with all the veins from one lung entering the right atrium has a physiologically useless lung. The perfection of an "extracorporeal heart" will some day allow the surgical correction of these (and many other) congenital defects.

Anomalies of the great mediastinal veins are not uncommon but are most often associated with other cardiac anomalies. Although a persistent left superior vena cava is in itself incapable of producing cyanosis, overriding of the aorta, pulmonary stenosis and septal defects are usually present in addition. Shown in Figure 7 are the right heart angiocardiograms of a seven year old girl whose only cardiac abnormality was an anomalous left innominate vein which passed beneath the arch of the aorta and the left pulmonary artery before crossing to the right to join the normally positioned superior vena cava.[9]

CYANOTIC CONGENITAL HEART DISEASE

The angiocardiographic study of the patient with a complex combination of cardiac anomalies offers a twofold challenge to the interpreter. The potential benefits of surgery in properly selected cases make correct interpretation a matter of more than academic importance. Secondly, given a technically adequate set of angiocardiograms, it is safe to assume that the films contain most of the information necessary for the anatomic diagnosis. Systematic interpretation directed toward identifying individual lesions constitutes a more logical and successful plan of approach than any immediate attempt to pigeonhole the patient's anomaly into one of the many pathologically sound but physiologically indistinct entities. For reasons already stated it is our belief that patients with cyanotic heart disease who are immediate candidates for surgery should be routinely studied by angio-

cardiography. Cardiac catheterization will frequently be unnecessary.

At The New York Hospital two projections, the frontal and lateral, are routinely employed in the study of the cyanotic congenital cardiac patient, two injections of contrast agent being necessary. (Specialized apparatus has made possible biplane, stereoscopic angiocardiography following a single injection.[48]) For young or uncooperative patients general anesthesia is employed. Diodrast 70 per cent, neo-iopax 75 per cent and urokon sodium 70 per cent have been used by us with comparable diagnostic results. The cumulative experience of the authors totals about 2,000 consecutive angiocardiographic examinations without a fatality.

Tetralogy of Fallot. Referred to as a tetrad, this anomaly consists essentially of the combination of two lesions, pulmonary stenosis (infundibular or valvular) and dextroposition or overriding of the aorta. A physiologic if not an anatomic interventricular septal defect always occurs when the aorta overrides the interventricular septum, and right ventricular hypertrophy is the result of pulmonary stenosis rather than a fundamental component of the anomaly.

The angiocardiographic identification of pulmonary stenosis in this and other cyanosis-producing anomalies may be direct or indirect.[49–53] In about half the cases an area of pulmonary infundibular or valvular narrowing is seen. In the remaining cases the presence of stenosis may be inferred with reasonable assurance from one or more of the following findings: (1) The pulmonary arteries are unusually small, (2) they fill poorly with opaque substance and (3) the central pulmonary arteries, even though fairly large and well filled, are irregularly deformed in appearance while the peripheral branches are disproportionately small. Even though good filling of apparently normal pulmonary arteries is seen, pulmonary stenosis cannot be excluded angiocardiographically (although in such cases it is reasonable to conclude that marked reduction in pulmonary blood flow is not present). Furthermore, failure of the pulmonary arteries to fill with contrast substance may be the result of transposition of the great blood vessels rather than pulmonary stenosis.

Dextroposition or overriding of the aorta is manifest in the angiocardiogram by the immediate passage of contrast agent from the right ventricle to that vessel, a direct angiocardiographic demonstration of the cause of the patient's cyanosis. In general, the degree to which the aorta over-rides can be estimated from two findings. If early aortic opacification is faint as compared to the density in the pulmonary artery and as compared to that obtained later in the angiocardiographic series when contrast substance reaches the aorta from the left ventricle, it may be assumed that but slight dextroposition exists.[53] Furthermore, the position of the base of the aorta with respect to the heart border and the contour of the aortic arch are of significance. The farther anterior the origin of the aorta and the more rounded-out its course through the thorax, the greater the degree of aortic overriding probably present. The angiocardiographic findings in a typical case of tetralogy of Fallot are illustrated in Figure 8. The so-called pseudotruncus arteriosus is a variant of the tetralogy of Fallot in which the pulmonary artery is markedly stenotic if not atretic, circulation to the lungs being via bronchial arteries.[51]

Pulmonary Stenosis and Interatrial Septal Defect. In the combined presence of pulmonary stenosis and a defect in the interatrial septum an overriding aorta may be simulated on angiocardiography. In this malformation blood passes across the septal defect from the right to the left atrium, via the left ventricle into the aorta, while at the same time blood entering the right ventricle through the tricuspid valve reaches the lungs through a stenotic pulmonary artery.[54,55] Cyanosis results. Angiocardiography reveals simultaneous opacification of the aorta and the pulmonary artery.[9] The diagnosis of dextroposition of the aorta is made less likely by the demonstration of a direct passage of contrast agent from the right to the left atrium on early films of the series. (Fig. 9.) This finding is not conclusive since an interatrial defect with reversal in the direction of blood flow may complicate the tetralogy of Fallot. Reflux of contrast agent into the inferior vena cava is common in this condition as in tricuspid stenosis or atresia but may also occur normally.[16] In pulmonary stenosis and interatrial septal defect the pulmonary arteries usually show poststenotic dilation and are emptied of contrast substance more slowly than is the aorta. Especially when the pulmonary stenosis is severe, cyanosis may be present from birth. In other cases cyanosis may be delayed in onset. This is because the pulmonary stenosis over a period of years has resulted

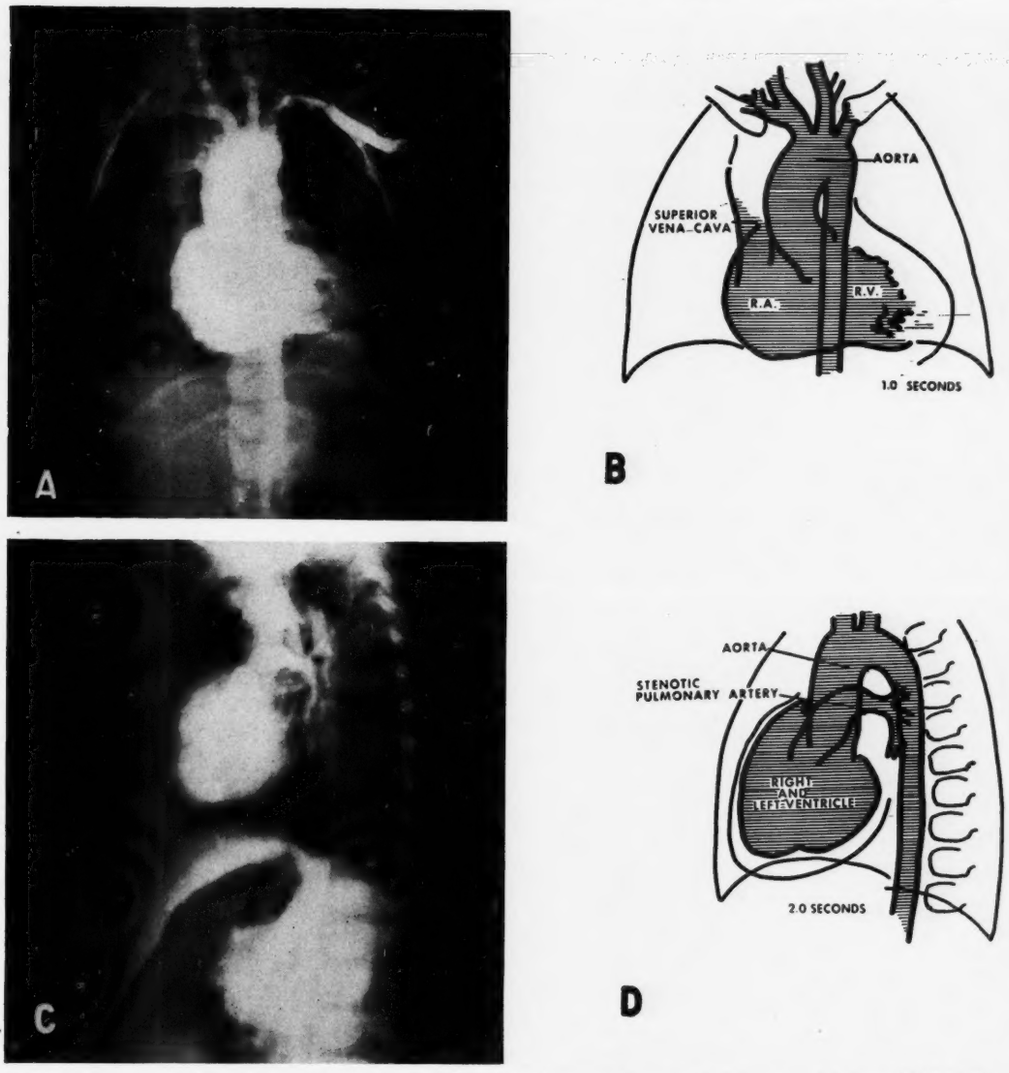


FIG. 8. *Tetralogy of Fallot—Dextroposed aorta and marked pulmonary stenosis:* A two year old male (562 557). Electrocardiogram showed right axis deviation. A, frontal angiocardiogram at 1.0 second. Very dense immediate opacification of aorta indicates marked dextroposition. Pulmonary arteries not visible. C, lateral angiocardiogram at 2.0 seconds. The medial point of origin of the aorta is against transposition. Both ventricles are filled. The pulmonary artery is very small. Electrocardiogram is against tricuspid stenosis. Marked improvement following Blalock-Taussig procedure. From DOTTER, C. T. and STEINBERG, I. Angiocardiography. New York, 1951. Paul B. Hoeber, Inc.

in a gradual elevation of the right ventricular end-diastolic and hence the right atrial pressure. When the latter exceeds the pressure in the left atrium, reversed flow across the defect (usually a patent foramen ovale) occurs and cyanosis results. Direct surgical relief of pulmonary stenosis by incision of the stenosed valve or punching out sections of the narrowed infundibulum may produce marked relief of symptoms.[56] Surgical technics vary depending upon the type of pulmonary stenosis present, and both angiocardiography and cardiac catheterization are of value in making the distinction.

Tricuspid Stenosis and Atresia. In severe tricuspid stenosis or atresia blood flow is from the right atrium across an interatrial defect into the left ventricle and thence to the aorta and pulmonary arteries. The origin of the great vessels may vary considerably. Both may arise from the left ventricle; either may arise from a diminutive right ventricle which receives blood from the left ventricle via an interventricular septal defect.[20] Pulmonary stenosis may occur as may an associated patent ductus arteriosus. As is illustrated in Figure 10, angiocardiography usually reveals the abnormal course of blood

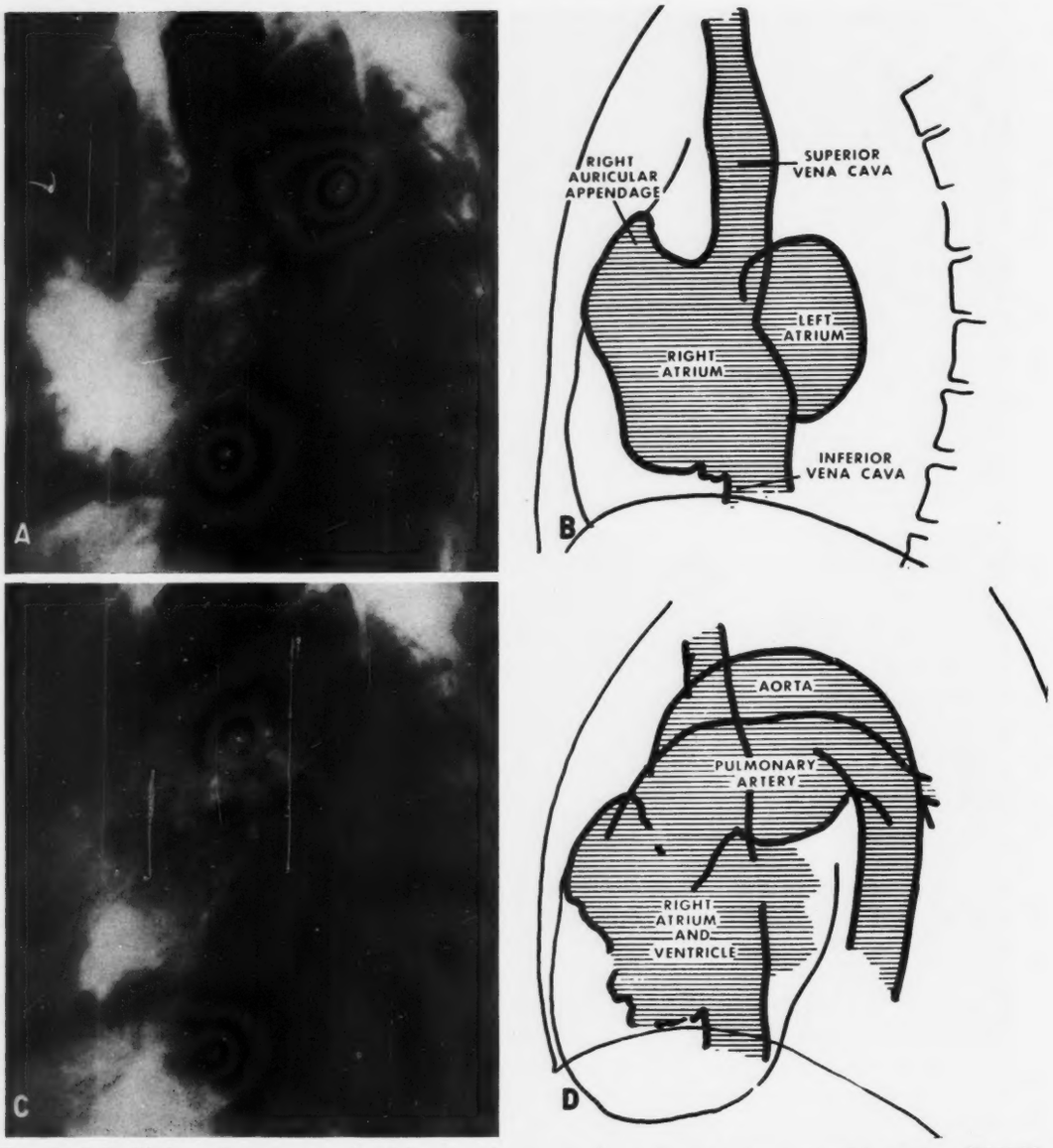
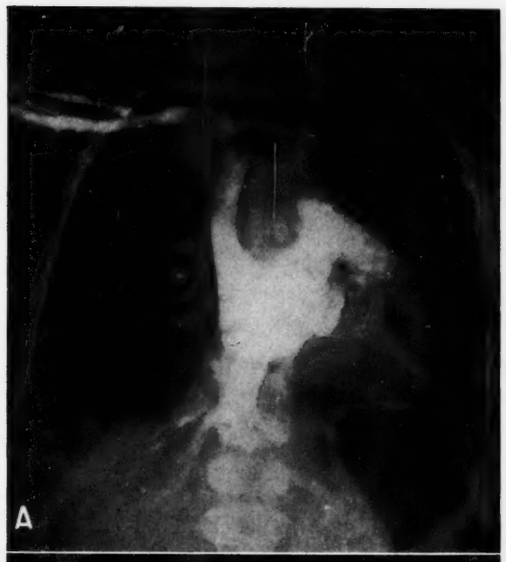
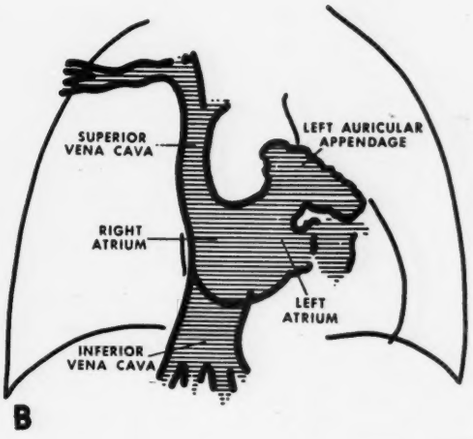
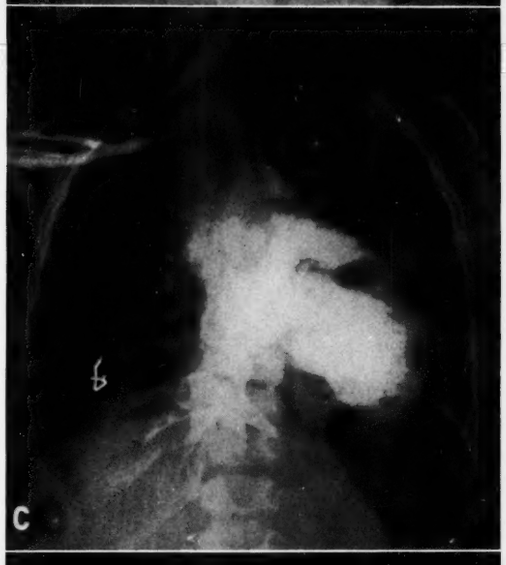


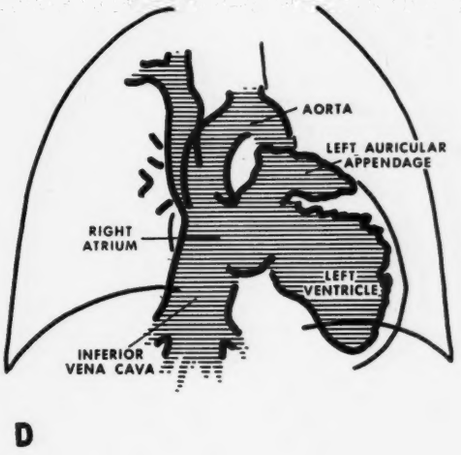
FIG. 9. *Infundibular pulmonary stenosis with patent foramen ovale:* A twenty-nine year old woman (N.Y.H. 571 401) had history of a cardiac murmur since birth. Dyspnea, increasing cyanosis and successfully treated subacute bacterial endocarditis six months previously. Cyanosis, clubbed fingers, loud systolic murmur and thrill were present. A, left anterior oblique angiocardiogram at 1.5 seconds shows direct spread of contrast agent from the right to the left atrium. C, at 3.5 seconds there is opacification of a markedly dilated pulmonary artery and faint filling of the aorta. Cardiac catheterization revealed a right ventricular pressure of 60/7 while that in the pulmonary artery was only 7/5. The patient did not survive attempted infundibular resection and subsequent autopsy confirmed the diagnosis.

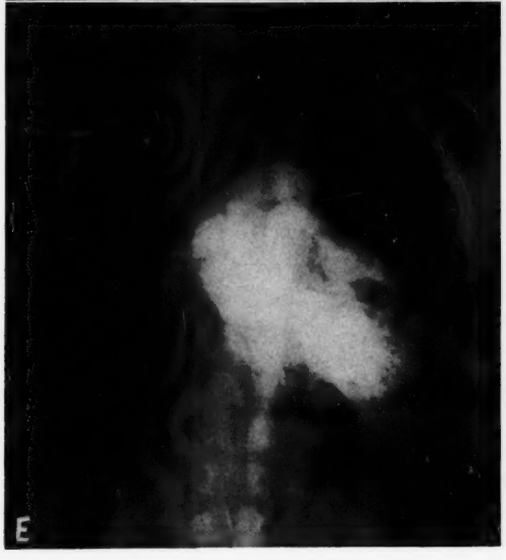
FIG. 10. Page 231. *Tricuspid atresia with transposition of the great vessels:* A five year old boy, cyanotic since two months of age. A left axis deviation was present on the electrocardiogram. Angiocardiographic series in frontal projection (A at 0.5 seconds, C at 1.0 seconds, E at 1.5 seconds) reveals direct spread of contrast agent from right to left atrium. The large aorta filled from a rudimentary right ventricle which apparently received blood from the left ventricle via an interventricular septal defect. The pulmonary arteries filled directly from the left ventricle and were unusually small, indicating pulmonary stenosis. Blalock operation resulted in clinical improvement. (The angiocardiograms used in this illustration were made available through the courtesy of the Department of Radiology of the Mount Sinai Hospital of New York City. The case has been reported in detail elsewhere.[58]











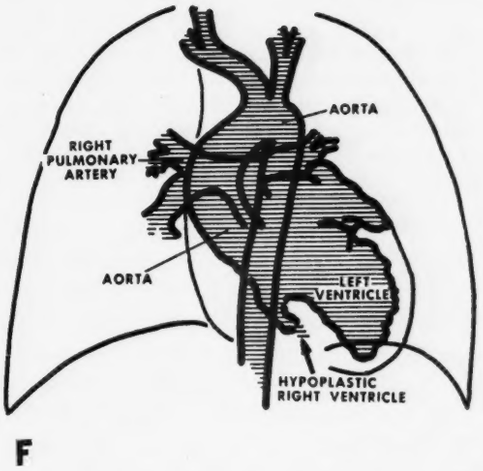


FIG. 10. See descriptive legend on page 230.

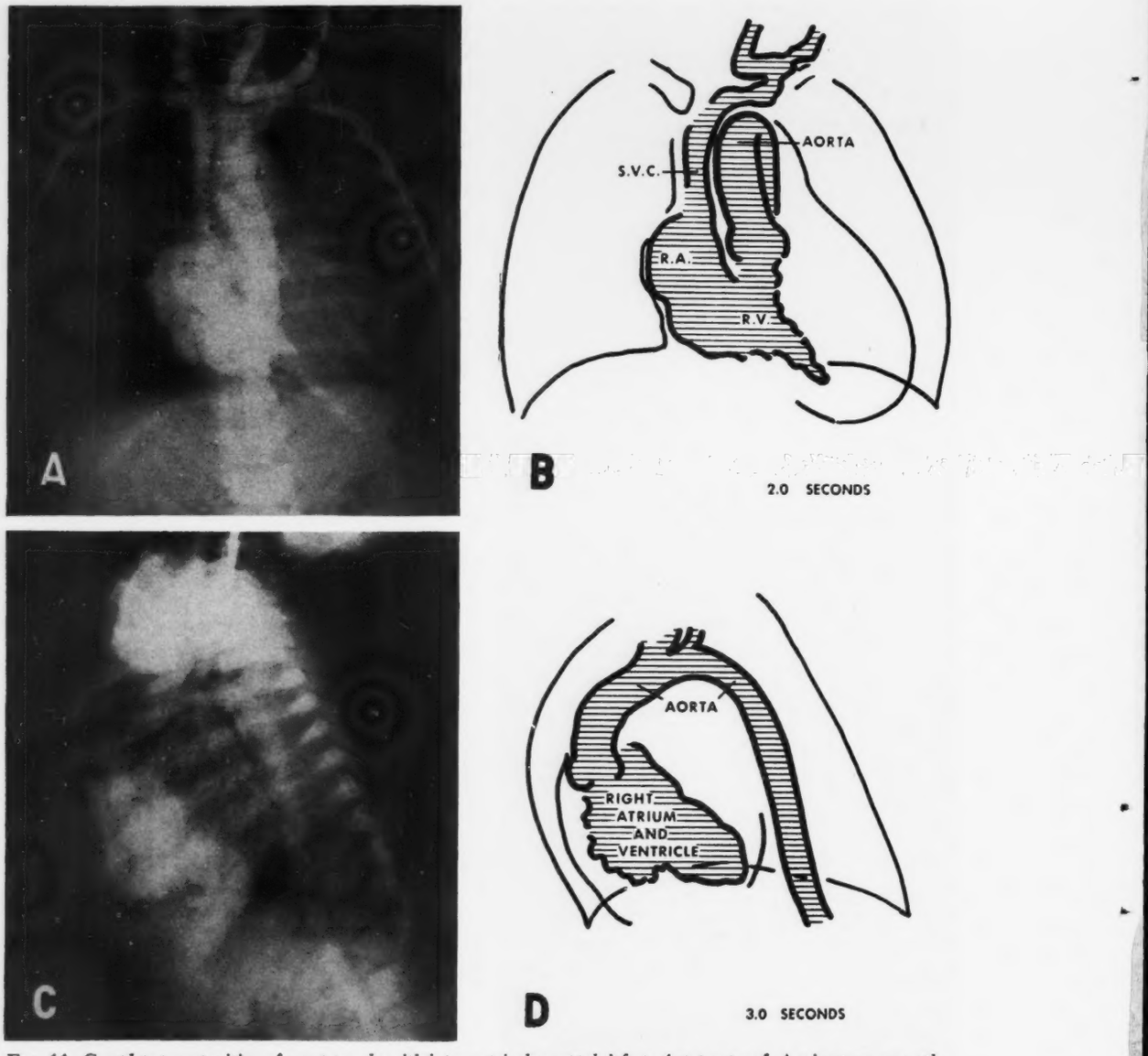


FIG. 11. *Complete transposition of great vessels with interventricular septal defect. Autopsy proof.* A nineteen month old child. A, frontal angiocardiogram at 2.0 seconds. Right ventricle and aorta filled. C, lateral angiocardiogram at 3.0 seconds. The opacified aorta is seen to arise far anterior and follow a wide, rounded intrathoracic course. The left ventricle and pulmonary arteries are not distinctly outlined. At autopsy in addition to transposition of the great vessels there was also an 0.5 mm. interventricular septal defect and probe-patency of the foramen ovale. (The angiocardiograms were made available by Drs. Robert Cooley and Robert Sloan of the Department of Radiology, The Johns Hopkins Hospital, Baltimore.)

flow clearly.[57,58] In this example the aorta takes origin from a diminutive, non-functioning right ventricle (filled via an interventricular septal defect) while the small pulmonary arteries give evidence of pulmonary stenosis. In another case reported elsewhere[9] tricuspid atresia was associated with dextrocardia, a common atrium, an anomalous pulmonary vein entering a left superior vena cava, a functioning single ("left") ventricle, severe pulmonary stenosis and a large patent ductus through which blood reached the lungs. All the anatomic features except the tricuspid atresia itself were clearly shown in the angiocardiogram. Since the diagnosis of tricuspid stenosis or atresia may be considered highly likely when cyanosis and a left axis deviation occur together, angiocardiography need be employed only when surgical procedures are contemplated or in atypical cases.

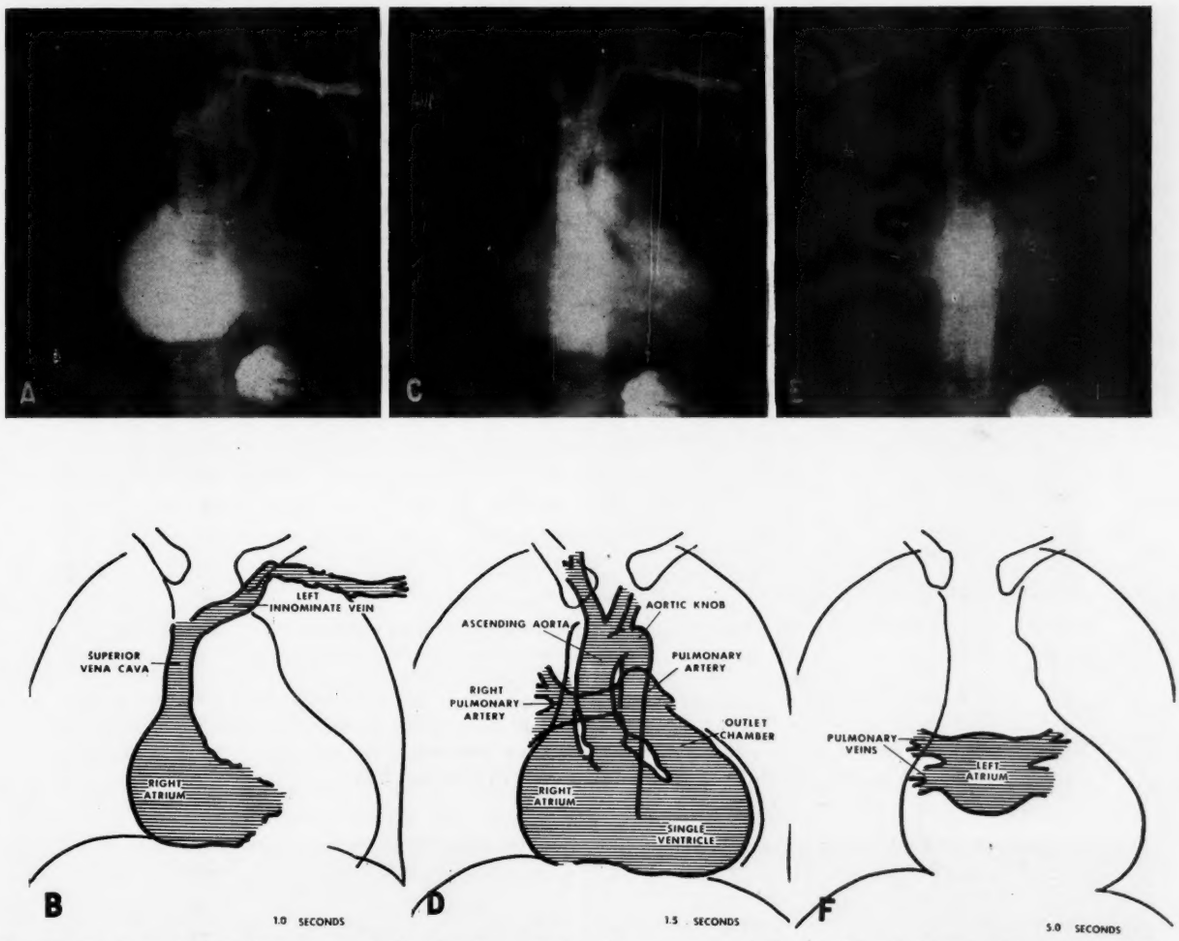


FIG. 12. *Single ventricle. Rudimentary outlet chamber giving off the pulmonary artery.* A five and one-half year old male (N.Y.H. 583 172). Cyanosis since three months. A, C and E, frontal angiocardiograms at 1.0, 1.5 and 5.0 seconds. The right atrium empties into a large single ventricle which gives rise to the aorta directly and to the pulmonary artery through a rudimentary outlet chamber. Pulmonary stenosis not demonstrated. Left atrium is normal. Diagnosis confirmed by cardiac catheterization.[61] From DOTTER, C. T. and STEINBERG, I. Angiocardiography. New York, 1951. Paul B. Hoeber, Inc.

Transposition of the Great Blood Vessels. It may be difficult to distinguish with certainty between extreme dextroposition of the aorta associated with severe pulmonary stenosis and complete transposition of the aorta and pulmonary artery, particularly when pulmonary stenosis complicates transposition. The aorta in transposition "takes off" far anteriorly and describes an open, rounded course through the upper thorax. (Fig. 11.) The density of contrast substance within the aorta closely approximates that within the right ventricle. If the pulmonary arteries appear prominent or unusually pulsatile at fluoroscopy and yet fill poorly or not at all during angiocardiography, transposition of the aorta and pulmonary artery should be strongly suspected.[59,60] When pulmonary stenosis is present, the diagnosis may be more difficult. Although in transposition of the great blood vessels life is dependent upon some intercommunication between the systemic and pulmonary circuits, these communications are rarely demonstrated at angiocardiography.

Single Ventricle. The authors' experience with the angiocardiographic findings in single ventricle is limited to but one case[9] in which the diagnosis could be considered reasonably certain. (Fig. 12.) Here the contrast substance outlined a large common ventricular chamber which gave rise directly to the aorta and through a rudimentary outlet chamber to a non-stenotic pulmonary artery. Findings at cardiac catheterization[61] were in agreement.

Eisenmenger's Complex. In this anomaly an overriding aorta is associated with pulmonary hypertension. The differential diagnosis be-

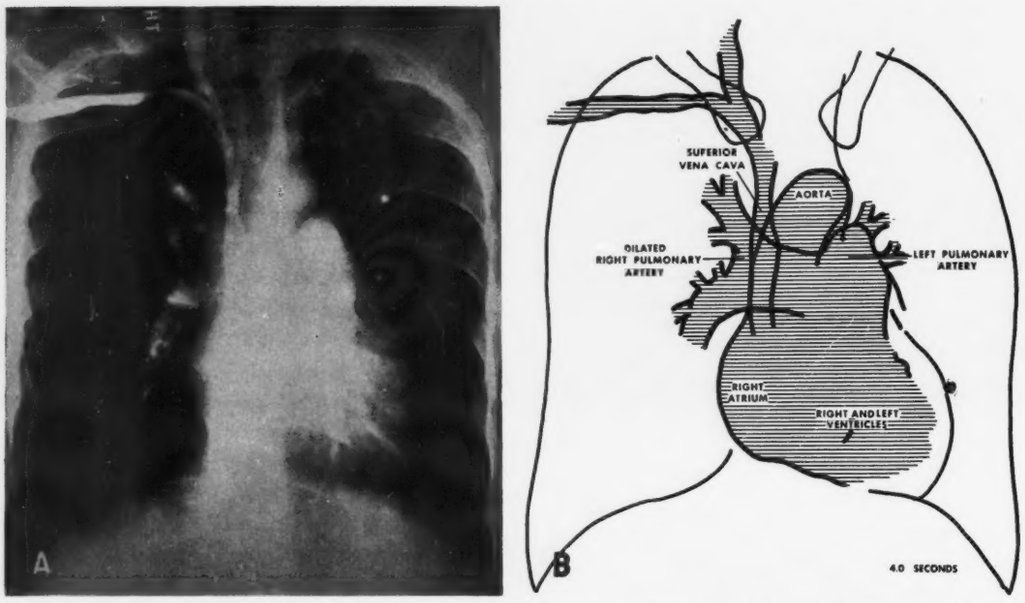


FIG. 13. *Eisenmenger complex—dextroposition of aorta; pulmonary stenosis excluded by cardiac catheterization:* A twenty-six year old male (N.Y.H. 568 155), cyanotic since infancy, recently increasing dyspnea, hematocrit, 78 per cent. A, frontal angiocardiogram at 4.0 seconds. There is opacification of both ventricles, the aorta, and markedly enlarged pulmonary arteries. At cardiac catheterization systolic pressures in the right ventricle, pulmonary and femoral arteries were found to be virtually identical. Without these findings, the diagnosis of Eisenmenger complex could not have been established. From DOTTER, C. T. and STEINBERG, I. Angiocardiography. New York, 1951. Paul B. Hoeber, Inc.

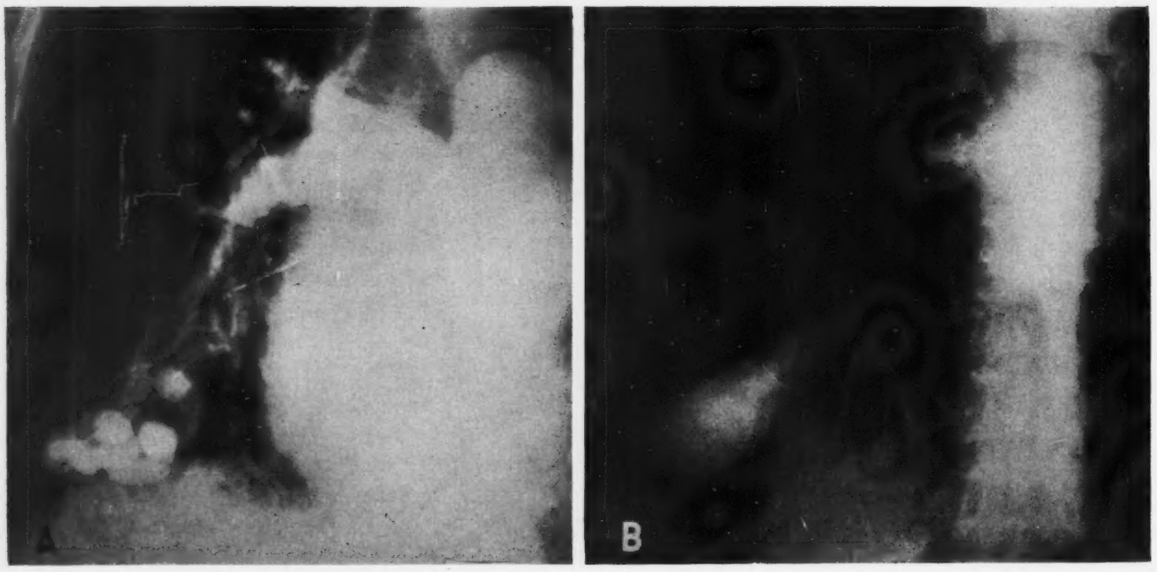


FIG. 14. *Pulmonary arteriovenous fistula:* A, frontal angiocardiogram at 4.0 seconds. A sixty-seven year old female (N.Y.H. 319 819) with rheumatic heart disease of many years' standing. The diagnosis was made on the basis of a conventional chest x-ray, strengthened by the demonstration of a bruit at the right base and proved by angiocardiography. B, frontal angiocardiogram at 5.0 seconds. The patient, a thirty-nine year old woman (N.Y.H. 596 001), was admitted for a brain abscess which was treated surgically. Chest x-ray showed a rounded mass in the right lower lobe with communicating vascular shadows. Diagnosis confirmed by opacification of the arteriovenous fistula which was fed by a branch of the posterior basal segmental artery and drained into the left atrium through a large pulmonary vein.

tween Eisenmenger's complex and a high interventricular septal defect with pulmonary hypertension is made with great difficulty by any available method. In two of our three cases there was angiocardiographic evidence of immediate aortic opacification (Fig. 13) while in the third case this was not observed. Immediate filling of markedly dilated pulmonary arteries was uniformly present. In each case cardiac catheterization revealed virtually identical systolic pressures within the right ventricle, aorta and pulmonary artery. In all cases the catheter was repeatedly passed from the right ventricle into the aorta. It is our belief that the Eisenmenger complex occurs more rarely than is commonly supposed. A diagnosis of Eisenmenger's complex cannot be considered proved on the basis of angiocardiographic evidence alone but must be substantiated by cardiac catheterization.

Pulmonary Arteriovenous Fistula. Although not properly a cardiac anomaly, the presence of a congenital fistulous or aneurysmal intercommunication between a branch of the pulmonary artery and a pulmonary vein causes cyanosis and polycythemia. In localized lesions resectional surgery is curative. Angiocardiography[16,47,62,63] sharply delineates the abnormal vascular channels (Fig. 14) and should be routinely performed prior to surgery, not only to outline the suspected lesion but also to demonstrate or exclude similar lesions elsewhere in the lungs. All of both lung fields should be examined, something not readily accomplished when small film sizes are used. A single 14 by 17 inch film of the chest made four seconds after the beginning of the angiocardiographic injection will suffice for this purpose. Interestingly, unlike peripheral arteriovenous communications, pulmonary arteriovenous fistulas do not cause an increase in cardiac output. For reasons not completely understood the pulmonary vascular resistance remains within normal limits despite the presence of the abnormal communication.[64]

Angiocardiography has proved itself to be indispensable in the complete study of congenital heart disease. The indications for the procedure as well as its shortcomings are now clearly defined. As in any problem in radiographic interpretation, a knowledge of normal anatomy and physiology coupled with respect for and understanding of pertinent clinical and laboratory data will greatly facilitate the interpretation of angiocardiograms.

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Clinic on Psychosomatic Problems

Diagnostic and Therapeutic Problems in a Patient with Epilepsy, Psychosis and Temporal Lobe Abnormality

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. WILLIAM H. TRETHOWAN: The patient is a thirty-six year old married man who has had three admissions to the Massachusetts General Hospital. The development and evolution of his illness are complicated and are perhaps best presented chronologically. Until four and a half years ago he was seemingly quite normal. The patient worked as a machinist and happened to be alone in the shop one day during lunch hour. His fellow workers returned to find him unconscious on the floor in a pool of blood, having a generalized convulsion. There was a laceration of the scalp in the left parieto-occipital region. He was taken to a hospital for treatment of the wound and for x-rays of the skull which were said to show no fracture. Next day he was discharged, apparently well except for the scalp wound. The patient could remember nothing of the accident and it was impossible to determine just what had happened.

Approximately two weeks later he commenced to have attacks which he described as blackouts. These came without any warning or aura and caused him to stop whatever he was doing for a few minutes or to carry out some action in an automatic way without awareness of what he was doing. He would recover within five minutes and frequently did not know that he had had a spell unless someone told him about it. Sometimes he discovered that something inexplicable had happened during the blackout as for example when he entered a bowling alley and shortly afterwards "came around" to discover that he had removed his outer clothing down to his shirt. On another occasion while driving his car he crashed into two parked automobiles without knowing it until after the collision. He was apprehended by the police on this account and his driving license was taken away from him.

The patient's wife said that these blackouts were frequent, occurring about two to three times weekly. He sometimes talked to himself in a repetitive manner, laughed or screwed up the left side of his face. Following the spell he would be quiet for five or ten minutes, then would become irritable and sometimes lose his temper. Besides these minor attacks, his wife stated that he had two major seizures of a grand mal type. After one of these he appeared dazed; and when his wife tried to get him to bed, he struck her. Later he had no recollection of the incident.

Following the onset of the minor attacks after the accident, the patient was given dilantin® in gradually increasing doses to 7 (0.7 gm.) capsules a day. He complained that the drug upset his stomach and made him nervous. The patient's wife has described a marked change in his personality since the onset of the illness. Previously jolly, happy, friendly and sociable, he became morose, "couldn't take a joke" and was "nervous." Prior to the illness his work record was good. Since he became sick he has been unable to work and has remained at home doing domestic chores and looking after the children. Furthermore, his sexual behavior was altered, his wife stating that intercourse took place only once every three or four months.

Three years after the first symptoms he was admitted to a state hospital for psychiatric observation. The report from this institution states that he presented the "irritable, childish, complaining personality of the interparoxysmal epileptic." There was further mention that he appeared garrulous, perseveratory, self-centered and rather sorry for himself. He was well oriented, his memory was unimpaired (except for the brief periods of the seizures), and there was no evidence of hallucinations or delusions. The

impression was that he was mildly deteriorated mentally but not to a certifiable degree. Accordingly he was discharged after ten days of observation.

Six months later (just about a year ago) he was admitted to the Massachusetts General Hospital where he complained (as he had done before) of unfair treatment by his employers regarding payment of his medical bills. He complained more or less continuously of disabling pain in the region of the scar on his head. Physical examination and neurologic examination revealed nothing abnormal. The electroencephalogram showed an abnormal record with a spike focus referred mainly to the right temporal region, with some involvement of the left side as well. An air encephalogram was done and was interpreted as indicative of a moderate degree of brain atrophy. The spinal fluid tests were all normal. A Wechsler-Bellevue Test indicated a limited intellectual endowment, the full scale I. Q. being 87.

During this admission to the hospital there was a change in the patient's behavior. His talk became aggressive and incoherent, frightening other patients in the ward. There was elation of mood and great concern with religious symbols. He talked a lot about God and said that he had important revelations from God to be transmitted to the President of the United States. The general impression of those who saw him at this time was of a schizophrenic type of illness. Following transfer to the Psychiatric Ward, he improved greatly within three days and was discharged shortly with a diagnosis of "epileptic confusional state."

The patient's general condition remained about the same and four and a half months ago he was readmitted to the hospital for further evaluation and study. The perseveration was marked at this time; he complained constantly of the pain in his head and how he had not received any compensation for his injury. It was only with great difficulty that he could be induced to talk of anything else. He spoke with an angry tone going over the same topic again and again. Once started he was not easily interrupted and his recitation of complaints was so stereotyped as to resemble a phonograph record playing the same thing over and over, endlessly.

The mental status was that of a psychotic, although the clinical picture was rather bizarre and "amorphous." It resembled paranoid schizophrenia more than anything else. In some ways, however, his restlessness and odd manner of talking suggested the possibility of organic dementia perhaps in association with the epilepsy or as a result of head injury.

Further EEG studies were undertaken using photic stimulation and subconvulsive amounts of metrazol. Myoclonic jerks were observed coincidentally with the spikes on the EEG tracing. Later a record taken while the patient was asleep showed notable spiking from the leads connected to the right and left temporal regions.

Medication with dilantin had been withdrawn, partly in order that the EEG studies could be better interpreted, and partly to assess the effect that the drug had had upon the patient. He had several seizures within a three-day period, expressed more paranoid ideas and became increasingly aggressive and uncooperative in the ward. The medication was resumed and after another week an operation was performed. This consisted of resection of the right temporal lobe to a point 5 cm. back as measured along the Sylvian fissure and 7 cm. along the base of the lobe.

The patient's postoperative course was uneventful. From the psychiatric standpoint he was noted (ten days after operation) to be much quieter and more apathetic than before. It was difficult to get him to talk freely, but once started his manner of speech was essentially the same as that previously noted. There was the same perseveration about his accident and his unfair treatment in regard to compensation but the press of talk was not so marked as before and interruption was now easier. It was still impossible, however, to induce him to discuss any other subject in a satisfactory manner.

It is now approximately fifteen weeks after the operation and again we have admitted the patient for evaluation of his condition. In the ward he has been quiet and well behaved. No attacks have been observed. We have not been able to obtain a detailed account of his status at home but apparently there have been none of the attacks associated with disturbed behavior as were described previously. Some minor attacks have occurred, probably of the petit mal type. The perseverative tendency still exists, but to a less degree, and ideas of reference continue. All in all, however, there is less "charge" —he is not so intense in his hostility and suspiciousness. He is more friendly and his affect is warmer.

We thought this patient was interesting be-

cause of the complexity of factors contributing to his illness and before presenting him to the group would like to have the comments of Dr. White who performed the operation and Dr. Abbott who interpreted the EEG studies.

Dr. James C. White: We thought it unwise to do the operation under local anesthesia, as we would ordinarily, because of his inability to cooperate. We were worried also about operating on the dominant hemisphere; and because it was necessary to use pentothal anesthesia,® we were not able to test by cortical stimulation the speech area. The amount of temporal lobe removed (5 cm. along the Sylvian fissure) is the amount stated by Penfield[1] which can be resected without producing aphasia in the dominant hemisphere. We had the story that he was completely left-handed.

Under light pentothal anesthesia we had applied EEG leads to the cortex to localize the areas where bursts of high voltage spikes were emanating. These were originating in the most posterior area that I dared resect, but I was able to remove this tissue where the abnormal spiking appeared and the remainder of the temporal lobe in front.

In one of the seizures observed preoperatively in the ward, the patient made smacking movements of his lips, suggesting involvement of the island of Reil. None of his seizures had made him aphasic and after operation there was no aphasia. Therefore, it is an open question whether the right hemisphere was the dominant one or whether dominance had shifted to the left hemisphere.

Dr. Stanley Cobb: How about the effect upon his seizures?

Dr. White: He had none during the two weeks in the hospital following operation. We noted a change in his supercharged speech and hostility. He was more docile and did not rant in a loud manner as before. He was quiet and apathetic as if we had done a radical resection of the frontal lobes. Doesn't that fit in with Percival Bailey's ideas that it is not so much the question of *where* you remove brain tissue, but *how much* that determines the patient's subsequent response?

Dr. John A. Abbott: When I saw him, about a year ago during his first admission here, he was agitated and I thought he was schizophrenic. The EEG studies revealed temporal lobe spikes. These have been predominantly on the right side, although to a less marked degree also on the left. The spike focus has shown a tendency to wander, but mainly has been concentrated at one point. This is characteristic of temporal lobe spikes.

The operating room recordings show sharper and briefer spikes. This is because the electrodes were placed directly on the cortex and there was not the resistance of intervening tissues present as when recording from the intact scalp.

After operation, spikes were absent on the right but still present on the left. The most recent EEG is still abnormal. There are some suspicious, sharp, spike-like waves on the right side (the operated side) but the only typical and characteristic spikes now come from the left temporal region.

Dr. Cobb: May we have a summary of the psychologic tests?

Mrs. Doris Gilbert: A year ago, during his first admission, he was very much frightened by what was happening to him (the delusions and paranoid ideas). He said when I tested him, "I will do anything; I will wash your feet." He was very rambling and distractable and in the Wechsler-Bellevue Test gave a poor performance, suggesting below average endowment with no suggestion that he had ever operated much better.

When tested again just before the operation he showed poor and often bizarre judgment with less rational control over performance. In the Rorschach Test he was preoccupied with personal ideas of a paranoid content which interfered with the test. The picture was primarily that of emotional turmoil with inability to give adequate responses because of perseveration and paranoid ideas.

Ten days after operation the Wechsler-Bellevue Test indicated that the operation had not lowered his intellectual abilities.

I tested him again (fifteen weeks after operation), giving the Rorschach and Wechsler-Bellevue tests. His performance in the latter was superior to any previous one. This could be due, in part, to learning the test or to the personality changes which were observed, i.e., less evidence of disintegration and improved control. There were some suggestions of apathy or dulling of emotional response. He did not show the responses typically seen in very seriously brain injured patients. He is, however, certainly below average for originality and again there is some

[1] Penfield, W. and Rasmussen, T. The Cerebral Cortex of Man. New York, 1950. Macmillan Co.

perseveration. His manner during the testing was agreeable, cheerful and childishly playful.

I would say in general that the tests show only slight cerebral impairment, none due to operation alone, but suggest a degree of simplification probably related to an immature personality with slightly below average intellectual endowment. I could not estimate adequately to what extent the impairment of his performance was due to effects of the disease process itself. (That is, the epilepsy or trauma or both.)

PRESENTATION OF PATIENT

The patient had a rather puzzled, vague expression but showed no reluctance in entering the conference room. When asked how he was feeling, he launched into a detailed story of the pain in his scalp, the injustice of his employers and his intention of suing them. Attempts by Dr. Cobb to get him to talk about other things were not successful. When Dr. White asked if the patient remembered him, he replied, "No," but then expressed his gratitude by seizing Dr. White's hand and kissing it repeatedly. It was only with difficulty that he was persuaded to go back to the ward.

STAFF DISCUSSION

DR. COBB: Do you remember the monkeys operated on by Klüver?[2] They stuck everything into their mouths. You saw what he did to Dr. White's hand. The monkeys became placid and oversexed. They were always mouthing everything.

He has not lost all of his aggression. As soon as I tried to interrupt him he got mad. I suppose he has always had a low intellectual level. It is hard to decide upon the relative importance of various factors: how much is his present condition the result of the accident, how much due to epilepsy and how much to poor endowment to begin with.

Has he changed sexually?

DR. TRETHOWAN: I have not been able to see his wife to inquire about that.

DR. COBB: I was going to ask him about it here, but I was afraid of precipitating an explosion. He still has plenty of aggression.

I think an interesting phenomenon here is that he has shown a rather special form of behavior which has been observed in a lot of people with lesions in the temporal lobes. The syndrome has been recently reviewed.[3] It has been called epileptic insanity, fugue, epileptic equivalent, automatism, dreamy state and has more recently been classified in that loose group called psychomotor epilepsy. Many of the symptoms have been helped by removal of the temporal lobe. In this man excision of the area which showed abnormal electrical activity caused marked improvement, but he is still a fairly abnormal man.

DR. TRETHOWAN: Psychiatrically he is the same as before operation, but with the soft pedal on. I was afraid previously that he might attack me, and the other patients were alarmed by him. To express in a figurative way the change after operation one might say that the same light is shining but the battery has run down a little.

DR. ABBOTT: We were not able to demonstrate waxing and waning of the psychiatric disturbance along with waxing and waning of the spikes in the EEG. However, I would assume that that was occurring. I am completely on the fence as regards the presence or absence of a schizophrenic component.

I do think that the improvement is related to the operation because of the removal of the electrically abnormal tissue.

DR. COBB: There was a report by Dr. John Green of Phoenix, Arizona, on a series of twenty-three temporal lobectomies. He brought out the point that the patients' psychotic manifestations were usually temporally related to waxing and waning of the epilepsy. After operation, not only was the epilepsy improved but also the patients' mental symptoms. In a number of others, however, the abnormal mental states went along without fluctuations; those were not helped mentally by the operation. We have not had enough experience with these latter patients. This patient of ours falls into that group. A recent paper by Jasper reports that about half of those with lesions or electrical abnormality (spikes) in one temporal lobe also have spikes in the other. That brings up the question of whether a bilateral operation might be recommended.

In this case I think there was evidence, even without the EEG, that there was a focus in the temporal lobe. The sort of fits, epileptic automatisms, are exactly like those described by

[2] KLÜVER, H. and BUCY, P. C. Preliminary analysis of unctions of the temporal lobes in monkeys. *Arch. Neurol. & Psychiat.*, 42: 979, 1939.

[3] COBB, S. Review of neuropsychiatry. *Arch. Int. Med.*, 87: 889, 1951.

Hughlings Jackson, especially the lip smacking during the fits. I prefer to use the term *epileptic automatisms* rather than the term *psychomotor epilepsy*. I think it is more descriptive and accurate to say that this man had epileptic automatisms and occasional convulsions.

DR. MARIA LORENZ: He has an obvious mental defect in terms of thinking and intellectual functioning. The persistence he shows in sticking to his story is something to protect him from the confusion he feels. He shows a common result of lobotomy—there is much emotion there that might explode, but he is quickly distracted from it. It might be likened to the "catastrophic reaction" described by Goldstein[4] in brain injured patients.

DR. HENRY H. W. MILES: In this type of epilepsy, what sort of histologic changes do you find?

DR. WHITE: There were not any in this case. I asked particularly that the pathologist make special stains for astrocytes, but no abnormal gliosis was found.

DR. COBB: There was no abnormality you could see. In many cases reported by Penfield and Flanigin[5] there were lesions; traumatic, superficial thickenings of the outer layers of the cortex. These were looked for in this man and were not present.

DR. AVERY D. WEISMAN: Have we any real definitive evidence that the psychiatric symptoms associated with these seizures have anything to do with the electrical abnormality? Should we consider that there is a localized focus and expect the operation to cure him? Will it be necessary to operate also upon the left temporal lobe?

DR. TRETHOWAN: The interesting point is that the focus may be considerably deeper in the brain and resonates through into one or both temporal lobes.

DR. COBB: The chances are that the epilepsy is genetic, of the so-called "idiopathic" type. He probably had a fit and hit his head in falling. Most patients with post-traumatic epilepsy do not have fits for several months or even years after the injury; his fits came within three weeks of his fall. Also, there was no histologic evidence of old injury in the removed tissue, and the abnormal electrical focus seems to be deep within the brain with a spread to the temporal lobes.

People who have fits immediately after trauma almost always have had epilepsy already. I think you can understand psychologically how a man like this, who has always been dull and frustrated by the problems of getting along in the world, would be further handicapped and frustrated by the added strain of unpredictable and frightening epileptic attacks. It is very easy for him to transfer the blame to the insurance company who will not pay him and the doctors who will not help him. He has superimposed upon his epilepsy a post-traumatic neurosis.

DR. ALFRED O. LUDWIG: Unfortunately we know very little about his pre-illness personality. As far as can be ascertained he was adequately adjusted and was working efficiently. However, as regards personality structure we know nothing. His psychiatric reaction may be similar to what Kardiner[6] describes, a breakdown with regression and primitive mechanisms. He seems to be a regressed person.

In post-traumatic neurosis you are apt to learn that the patient's pre-traumatic status was that of the "best workman in the place." If there was a particularly hard or dangerous job, he did it. This is an indication of the patient's use of overcompensation as a defense mechanism against anxiety and feelings of inadequacy. Then when the trauma (emotional or physical) destroyed the patient's defense, he became incapacitated by the neurosis.

DR. COBB: This man has raised a lot of interesting discussion about trauma, post-traumatic reactions and epilepsy. I think there is some risk that he might hurt someone and believe that social service ought to maintain a relationship with his wife so that we may have reports on his condition. If he becomes more aggressive and the EEG is showing more spikes, we should consider resection of the other temporal lobe. It is possible that he may have to be in a state hospital for the rest of his life. There are epileptics who need such care. He certainly has changes in personality typical of a certain group of severe epileptics. But I think the frequently used term "epileptic personality" is unfair and harmful to those many epileptics in the community who have normal personalities and get along well except for their attacks.

[4] GOLDSTEIN, K. The Organism. New York, 1938. American Book Co.

[5] PENFIELD, W. and FLANIGIN, H. Surgical therapy of temporal lobe seizures. *Arch. Neurol. & Psychiat.*, 64: 491, 1950.

[6] KARDINER, A. The Traumatic Neuroses of War. Psychosomatic Medicine Monograph II–III, National Research Council, Washington, D. C., 1941.

COMMENT

This case was presented to bring out some of the problems involved in understanding a severely disturbed patient with epilepsy. The simple concept of "epileptic personality" or "epileptic deterioration" does not do justice to the complexity of the manifold, interrelated etiologic factors.

First of all, there was a cerebral dysrhythmia manifested by episodic bursts of abnormal electrical activity (the EEG spikes) and by seizures. The latter were usually of the type commonly called *psychomotor epilepsy*, but generalized convulsions occurred on rare occasions. The discussion brought out the association between temporal lobe abnormalities and states of confusion and dreaminess. However, there were other aspects of the illness which were not consistent with the episodic nature of the electrical abnormalities in the brain. There was the severe personality disturbance with constant preoccupation about the injury and the bizarre paranoid manifestations. Theoretically, if one knew the patient's pre-illness personality, one might understand the psychosis much better. As was pointed out in the discussion, the psychologic trauma of an incapacitating and unpredictable disease may precipitate a severe neurotic breakdown (traumatic neurosis) with marked regression and primitive mechanisms (psychotic mechanisms). Unfortunately, the patient was never able to discuss anything but his current complaints, and it was not possible to get accurate and detailed data concerning his pre-psychotic personality structure. It was known that his intellectual endowment was sub-normal which probably also contributed to his psychologic vulnerability. Some of the perseveration may have been an attempt to "hold on" to the thread of his story, to protect himself from the confusion and anxiety which were so strong.

In any severe and frightening disease patients feel a strong need to put the blame somewhere. One frequently finds a patient with cancer, for example, or coronary artery disease, who is convinced that the illness is the result of some misbehavior on his part. In this case the head injury served as the scapegoat. It is worth emphasizing that the patient's intense neurotic preoccupation with his injury was not a voluntary matter but was determined by forces of which he was not consciously aware. (This is the essential difference between a traumatic or compensation neurosis and malingering.)

The rationale of temporal lobectomy was brought out in the staff conference. For those readers interested in a more extensive treatment of this problem, a number of references are mentioned[7,8] as well as others referred to in the discussion.

[7] MORRIS, A. A. The surgical treatment of psychomotor epilepsy. *M. Ann. District Columbia*, 19: 121, 1950.

[8] BAILEY, P. and GIBBS, F. A. The surgical treatment of psychomotor epilepsy. *J. A. M. A.*, 145: 365, 1951.

Clinico-pathologic Conference

Aortic Aneurysm, Hypertension, Heart Failure and Sudden Death

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. D. (No. 188276), was a Negro garage attendant, forty-four years of age, who entered the Barnes Hospital on August 8, 1950, complaining of shortness of breath.

The family history was non-contributory. The patient had enjoyed good health most of his life except for a brief episode of jaundice when he was twenty years of age. The systemic review was entirely negative. The patient had worked as an automobile mechanic, and since the onset of his illness had been assigned to lubricating cars. He had been married twice. No children had been born of either marriage and neither wife had had a miscarriage. For two years prior to the onset of his symptoms he drank a pint of whiskey daily.

At the age of twenty the patient developed a penile sore for which he sought no treatment. Ten years later he received approximately 150 intramuscular and intravenous injections but he was never told the results of this therapy. Four years before admission he suffered a rather sudden episode of dizziness, and although he did not lose consciousness he was unable to maintain his balance. He was seen by a physician who told him that his blood pressure was elevated; no therapy was given at this time. The patient then felt quite well for three more years except for occasional recurrent dizziness. One year before entry he began to have progressive shortness of breath on exertion. Several months after the onset of dyspnea he was unable to lie flat in bed and had to use two pillows for comfort. Six months before entry symptoms characteristic of mild paroxysmal nocturnal dyspnea developed. The patient was forced to sit in a chair all night, but nonetheless lost no time from his work. Two months prior to admission he came to the Medical Clinic. His heart was found to be greatly enlarged to the left, and a diastolic murmur was heard over the aortic area and at the apex. His blood pressure was 215/110. A few moist rales were present at the lung bases, the liver was moderately enlarged, and there was slight dependent edema noted. Urinalysis revealed a trace of albumin. The blood Kahn test was negative. The patient was treated with digitalis and a low salt diet and improved over a period of several weeks. Then signs of heart failure reappeared and the patient was sent into the hospital.

Physical examination at the time of entry revealed the temperature to be 37.2°C., pulse 110, respirations 26 and blood pressure 240/140. The patient was dyspneic and orthopneic but not cyanotic and he did not cough. No edema was present. The pupils reacted to light and accommodation and the eye grounds were entirely normal. Examination of the upper respiratory tract was negative. The neck veins were not distended. The lungs were clear except for occasional basal rales. The heart was markedly enlarged with a diffuse apical impulse visible and palpable in the sixth interspace, 15 cm. to the left of the mid-sternal line. A few ventricular premature contractions and a transient gallop rhythm were heard. The aortic second sound was loud and was followed by a high-pitched, early, blowing diastolic murmur which was transmitted down the left sternal border. There were no murmurs audible at the apex. The peripheral pulses were full but not collapsing. Neither a capillary pulse nor a pistol shot sound was elicited. Although the liver dullness was percussed 4 cm. below the right costal margin, the edge could not be felt. The remainder of the examination was negative.

The laboratory findings were as follows: Blood count: red cells, 5,180,000; hemoglobin, 15.5 gm.; white cells, 9,200; differential count: normal. Urinalysis: negative. Stool examination:

negative. Blood chemistry: non-protein nitrogen, 27 mg. per cent; sugar, 73 mg. per cent; chloride; 100 mEq./L; carbon-dioxide combining power, 27.5 mEq./L; total protein, 7.6 mg. per cent; albumin, 4.2 gm. per cent; globulin 3.4 gm. per cent; cephalin-cholesterol flocculation test, negative; thymol turbidity, 1.5 units. Circulation time (decholin): 22 seconds. Venous pressure: 178 mm. water. Vital capacity: 71 per cent of normal. Kolmer-Wassermann complement fixation test: negative. Cardiolipin test: negative. Roentgenogram of the chest: there was marked cardiac enlargement, primarily left ventricular; definite lengthening and dilation of the aorta with a superimposed saccular aneurysm at the distal transverse arch was noted. There was calcification within the aneurysmal sac. The lung fields were clear. Electrocardiogram: depression of S-T segments in leads I, AVL, V_2, V_4, V_5 and V_6; left ventricular enlargement; horizontal position of the heart; digitalis effect.

Shortly after the patient's entry a lumbar puncture was performed. The dynamics were normal and the spinal fluid was entirely negative. On the usual regimen for correction of cardiac decompensation the patient did quite well, losing 9 pounds during the two weeks he remained in the hospital. His renal function was evaluated and found to be relatively good. The results of the concentration diuresis test were within normal range. The patient excreted 70 per cent PSP in two hours and urea clearance was within normal limits. Intravenous pyelograms revealed no abnormality. The blood pressure fell to 180/100. The patient was seen in consultation by the neurosurgical consultant who advised sympathectomy, but the patient refused operation. While he was in the hospital, the patient was started on antisyphilitic therapy, first with bismuth subsalicylate and subsequently with penicillin. He was discharged on September 9, 1950, to be followed in the Medical Clinic.

The patient did relatively well on a cardiac regimen. On his visits to the clinic he appeared quite comfortable. On October 20, 1950, about five weeks after discharge, the patient noted a sensation of pressure in his chest shortly after he finished lunch. The pain persisted until about 9 P.M. when, while visiting a friend, the patient suddenly fell to the floor and was unresponsive for about one-half hour. His skin was cold and wet but he exhibited no convulsive movements. He was brought to the Emergency Room of the Barnes Hospital by which time he had become somewhat responsive. He complained of pain over the left lower anterior chest, and appeared to achieve some relief when he assumed the knee-chest position. He was immediately admitted to the hospital.

Physical examination revealed a temperature of 37°C., pulse 82, respirations 22 and blood pressure 120/70. The significant changes from those noted on the previous examination included dullness to percussion over the lower three-quarters of the left chest where the breath sounds and tactile fremitus were decreased. The heart sounds were distant and of poor quality; the rhythm was regular. The aortic diastolic murmur previously heard was only faintly audible but a soft apical systolic murmur was noted.

The laboratory findings were as follows: blood count: red cells, 3,750,000; hemoglobin, 11 gm., white cells, 7,950; differential count: segmented forms, 70 per cent; lymphocytes, 22 per cent; monocytes, 8 per cent. Urinalysis: negative except for a faint trace of albumin. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 30 mg. per cent; carbon dioxide combining power, 31.7 mEq./L; chloride; 106 mEq./L; prothrombin time, 60 per cent of normal. Venous pressure: 115 mm. of water. Roentgenogram of the chest; the saccular aneurysm in the transverse aorta had increased in size since the last film, and there was evidence of fluid in the left pleural cavity. Electrocardiogram: T waves inverted in leads I, AVL, V_2, V_3 and V_4; S-T segments depressed in V_1, V_2, V_3 and V_4; left bundle branch block; ventricular premature contractions; horizontal position of heart.

On entry the patient was given digitalis and sedatives and was maintained at complete rest. These measures resulted in improvement of his condition, and three hours after entry his pulse was stronger, he was free of pain and his blood pressure had risen to 140/90. On the morning after entry the red blood cell count was 3,670,000 with 10.5 gm. of hemoglobin. The patient continued to improve throughout the day. The peripheral pulses were equal and strong; the heart rate was 120. The heart sounds were more audible and of better quality and the patient rested comfortably. He had no dyspnea or orthopnea; and although during the day he coughed up small amounts of white mucoid sputum, the sputum at no time contained blood. The blood pressure fluctuated from 140/80 to

220/100 but the patient exhibited none of the signs of shock. A repeat electrocardiogram showed distinct changes from that obtained on the previous evening at the time of entry in that there was no longer bundle branch block; further, counterclockwise rotation of the heart had appeared, and there were changes consistent with anterior myocardial ischemia. Because the patient's temperature rose during the course of the day to 38°C., he was given aureomycin. On the third hospital day he remained comfortable and there were no significant changes in his condition. A quantitative blood Kahn test was reported as positive, with a titer of 20 Kahn units, and the Kolmer-Wassermann test was positive. During the evening of the third day the patient complained that his heart was "skipping." Auscultation revealed that there was an occasional ventricular extrasystole; the sounds were of fair quality. Aside from a fall in the red blood cell count to 2,740,000 with 10 gm. of hemoglobin, there was no change in the patient's condition until the morning of the sixth hospital day. During the previous night he had slept fitfully but had no other complaints. At 6 A.M. on October 25, 1950, when the patient was seen by a nurse, his temperature was 37°C., pulse rate 84, respirations 18 and blood pressure 230/120. Very soon after these observations were made he suddenly uttered a loud groan, became pulseless and expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient was thought to have a syphilitic aortic aneurysm, a diagnosis which seems tenable on the basis of the evidence available. Dr. Scott, do you agree with the clinical diagnosis?

DR. VIRGIL SCOTT: Yes, I do.

DR. ALEXANDER: I wonder if you would tell us something about the natural history of syphilitic cardiovascular disease? You will recall that this patient had a penile sore when he was twenty. Although he received no treatment until ten years later, he enjoyed good health for a period of at least twenty years. About one year before entry he developed signs of heart failure and died about a year after the onset of these symptoms.

DR. SCOTT: This case represents a typical example of the natural history of cardiovascular syphilis which develops in 10 to 12 per cent of patients with untreated syphilis. The average period between the primary lesion and the development of signs of heart disease is usually about twenty years. It is believed that the spirochetes gain entry into the adventitia and media of the aorta during early syphilis when general invasion by the organisms occur. Presumably nests of spirochetes persist in the aorta for years, gradually destroying the elastic tissue. Eventually sufficient damage is produced so that either the insertion of the aortic cusps is relaxed, giving rise to syphilitic aorta regurgitation, or else the wall of the aorta is weakened and an aneurysm develops.

DR. ALEXANDER: During the period of years when such a patient apparently is well, activity of the syphilitic process is continuing then?

DR. SCOTT: Yes, the process is only slowly progressive. It remains clinically latent and there may be no way to predict, on the basis of physical examination, that active aortitis is present. Only when the process becomes advanced far enough to produce either aortic regurgitation or dialatation of the aorta, does the physician find signs which enable him to make an unequivocal diagnosis of syphilitic aortitis, although it may be suspected earlier.

DR. ALEXANDER: It was of some interest that the many serologic tests performed on this patient were negative until three days before he died. At that time positive results were first obtained. Would you comment on this point?

DR. SCOTT: In untreated cardiovascular syphilis, with the sensitive technics now available, approximately 95 per cent of patients would be expected to have positive tests. This patient, however, received an unknown amount of therapy which may well have had an effect in lowering the reagin content of the serum. It may have become so low as not to have been detectable by insensitive tests such as have been used in the past, or even by a sensitive procedure like the cardiolipin test on a day when the latter was slightly less sensitive than usual. The sensitivity of all these tests is variable. I believe that it was unlikely that there was a change in the reagin content of the patient's serum. I would assume, therefore, that the positive results recorded shortly before the patient's death were due either to the fact that the sensitivity of the tests was a little greater than usual on that particular day or that the positive report referred to serum from a patient other than the one which we are discussing, in other words, a technical error.

DR. ROBERT J. GLASER: How often is variation in sensitivity apt to occur, Dr. Scott?

DR. SCOTT: The sensitivity of serologic tests for syphilis varies from one laboratory to another, and even in the same laboratory from day to day. These laboratory variations are responsible for the divergent results which are frequently reported, particularly in patients with low serum reagin levels.

DR. ALEXANDER: You nonetheless believe that the clinical diagnosis of syphilitic cardiovascular disease with a syphilitic aneurysm is quite likely here?

DR. SCOTT: There is no question in my own mind about it. One of the primary points in favor of the diagnosis is the fact that the patient had a saccular aneurysm of the thoracic aorta. It is extraordinarily rare for any process other than syphilis to lead to a saccular aneurysm in the thoracic aorta. Arteriosclerotic aneurysms occur rarely in this area; they are more common in the distal portion of the abdominal aorta. Mycotic aneurysms usually do not involve major blood vessels of the size of the aorta. On statistical grounds, therefore, there would be little chance that an aneurysm such that this man presented could be due to anything except syphilis.

DR. ALEXANDER: On his first admission, the patient was begun on bismuth therapy with the intention of giving him penicillin subsequently. I presume that bismuth was given first in order to avoid a Herxheimer reaction. Would you comment on the treatment of choice in cardiovascular syphilis? Is there real danger in giving penicillin without previous bismuth?

DR. SCOTT: The concept that it is dangerous to treat cardiovascular syphilis with penicillin unless previous preparation with bismuth has been carried out is based on unsound evidence. Shortly after the introduction of arsphenamine a number of instances was reported in which patients died suddenly while receiving an injection of arsphenamine or immediately thereafter. Such deaths were attributed to inflammation of syphilitic lesions about the coronary ostia. Actually when arsphenamine was first introduced, the toxic potentialities of the drug were rather great, perhaps due to impurities. These early unfortunate reactions were probably nitritoid crises rather than Herxheimer reactions. It has become increasingly clear, especially on the basis of recent evidence, that there is little or no danger in cases of cardiovascular syphilis when penicillin is begun immediately in any dosage. In certain types of neurosyphilis in which the pathologic process is somewhat different, caution may be indicated. In paresis, for example, spirochetes are present in the central nervous system in large numbers, whereas it is extremely difficult to demonstrate them at all in aortic syphilis. It may be that the Herxheimer reaction bears some relation to the number of spirochetes present in a given lesion although this possibility is by no means proven. It is fair to say, however, that Herxheimer reactions in cardiovascular syphilis, if indeed they do occur, are rare. For this reason it is perfectly permissible to institute penicillin therapy in the usual dosage as soon as the diagnosis of cardiovascular syphilis is made.

DR. ALEXANDER: That information is very enlightening, Dr. Scott. Certain textbooks still contain erroneous statements in regard to the dangers of cardiovascular Herxheimer reactions.

DR. HENRY A. SCHROEDER: I would like to ask Dr. Scott two questions. Can one stop the process of an aneurysm when it reaches the size noted in this man, and what is the current status in regard to wiring of syphilitic aneurysms?

DR. SCOTT: The first question cannot be answered definitely on the basis of information available to date. The best of the older studies[1,2] suggest that therapy may be beneficial in some instances, although I am not convinced that selection and other factors did not operate in these studies to produce the apparent favorable effect attributed to antisyphilitic treatment. The microscopic studies of the aortas of treated patients and untreated patients by Webster and Reader[3] also suggest a favorable effect. Until a definite answer to this problem is obtained, it seems to me that all patients with cardiovascular syphilis should be given the benefit of treatment with penicillin. I have had no personal experience with wiring of aneurysms or with cellophane wrapping. I am familiar with Blakemore's results which were apparently favorable in some

[1] MOORE, J. E., DANGLADE, J. H. and REISINGER, J. C. Treatment of cardiovascular syphilis. Results obtained in 53 patients with aortic aneurysms and in 112 with aortic regurgitation. *Arch. Int. Med.*, 49: 879, 1932.

[2] Grant, R. T. After histories for 10 years of 1000 men suffering from heart disease. *Heart*, 6: 275, 1933.

[3] WEBSTER, B. and READER, G. G. The effect of antisyphilitic treatment on the microscopic appearance of syphilitic aortitis. *Am. J. Syph., Gonor. & Ven. Dis.*, 32: 19, 1948.

instances. I believe Dr. Hunter can comment about these studies.

DR. THOMAS H. HUNTER: I saw some of the patients whom Dr. Blakemore operated upon, and I think the prevailing opinion was that some of them were definitely improved as a result of the procedure. Several patients who had developed tracheal compression because of aneurysm were particularly improved, and their lives were apparently prolonged for a number of years after the operation.

DR. ALEXANDER: Dr. Smith, this patient had obvious aortic insufficiency. Do you believe that it was due to syphilitic valvulitis?

DR. JOHN R. SMITH: That is by far the most likely explanation for the murmur. It is true that aortic insufficiency may arise in the course of severe hypertension, but in the presence of obvious syphilis of the aorta it seems to me that the valvular lesion should be attributed to syphilis also.

DR. ALEXANDER: The patient certainly had marked hypertension. Is there any way that one can distinguish on clinical grounds between aortic insufficiency due to syphilis and that due to hypertension?

DR. SMITH: No, the physical signs are identical in many instances.

DR. HUNTER: Is it not true, however, that if a given patient has signs of free aortic insufficiency, syphilis rather than hypertension would be the more likely cause?

DR. ALEXANDER: Yes, I would agree with you Dr. Hunter. In aortic insufficiency due to hypertension the diastolic pressure never reaches very low levels because the aortic valve *per se* is not abnormal. Dr. Massie, do you have any comments on this point?

DR. EDWARD MASSIE: I believe one can make a good case here for dilatation of the aortic ring on the basis of the syphilitic aneurysm and the marked hypertension. I would not be surprised if the patient had no syphilitic involvement of the aortic valve.

DR. SCHROEDER: One point in favor of this murmur having been due to syphilis is the fact that although the murmur became much less audible when the patient's blood pressure fell to normal, it was still present. Usually, the aortic diastolic murmur due to extreme hypertension disappears when, for any reason, the blood pressure attains normal levels.

DR. ALEXANDER: If a patient who had syphilitic aortic valvulitis also had extreme hypertension, would you not expect a rather marked lowering of the diastolic pressure?

DR. SCHROEDER: Yes, I would.

DR. SMITH: In regard to the fact that the patient's murmur decreased markedly when the blood pressure fell to normal, I should like to point out that patients with syphilitic aortic insufficiency of very mild degree may lose their murmur when they are kept at bed rest.

DR. W. BARRY WOOD, JR.: I believe great emphasis should be placed on the diastolic pressure in this case. If the patient had syphilitic aortic valvulitis at all, in my opinion it was minimal, and I do not believe that the anatomic changes of free aortic insufficiency will be found. Had they been present the diastolic blood pressure would have been much lower. I would agree, however, that the fact the diastolic murmur could still be heard when the patient's pressure fell to normal levels suggests that there was slight syphilitic valvulitis.

DR. ALEXANDER: What is your opinion in this regard, Dr. Scott?

DR. SCOTT: I believe that any Negro male of this age who had syphilis of long duration and an aortic diastolic murmur must be considered to have syphilitic valvulitis until proven otherwise. This patient certainly had syphilitic aortitis involving the transverse arch. I think it most likely that the process also involved the ascending arch, for syphilis tends to involve the proximal aorta primarily and is less frequent in the more distal portions of the aorta. Thus knowing that involvement of the transverse arch exists, one would anticipate that more proximal portions of the aorta would also be affected.

DR. ALEXANDER: Let us now consider the final events in the patient's illness. He apparently got along well on the usual therapy for heart failure until he developed severe pain in his chest which lasted for nine hours. He seemed then to improve, and he maintained a rather satisfactory clinical state until six days after entry when he suddenly died. Dr. Moore, what is your interpretation of this series of events?

DR. CARL V. MOORE: Since the patient had pain in his chest and subsequently developed signs of fluid in the left lower lung field, concomittantly with which his red cell count and hemoglobin fell, I think one has to assume that he bled into the pleural space. I believe that the patient's aneurysm ruptured. I am a little puzzled, however, as to why the bleeding did

not continue; it is difficult to explain why he lived for five days. Another possibility, of course, is myocardial infarction with subsequent rupture of the myocardium, but I think the latter is less likely.

DR. ALEXANDER: Are there any other comments?

DR. HUNTER: In my opinion either the patient's aneurysm ruptured, or the aneurysm eroded another vessel which gave rise to the bleeding into the pleural space. I favor the former.

DR. WOOD: I would like to ask the radiologist if he is certain that the patient had a saccular aneurysm?

DR. ROBERT S. LACKEY: The evidence is certainly in favor of that fact. It is true that the ascending aorta appeared to be of normal diameter of the earlier films and subsequently seemed to have enlarged slightly. That change brings up the possibility of dissection.

DR. WOOD: The possibility of dissection complicates this problem. Is it not true, Dr. Scott, that syphilitic aneurysms rarely if ever dissect?

DR. SCOTT: They certainly do not give rise to dissection in the usual sense of the word.

DR. WOOD: An explanation for the patient's terminal illness could be made on the basis of dissecting aneurysm, but in view of the fact that the evidence is overwhelmingly in favor of this having been a saccular aneurysm, I do not believe that one can reasonably pursue the former possibility.

DR. ALEXANDER: How would you have explained the clinical findings on the basis of dissecting aneurysm?

DR. WOOD: Dissecting aneurysm may begin in various parts of the aorta and may dissect either distally or proximally, or both. If this patient had had a dissecting aneurysm, it is conceivable that the dissection may have given rise to distortion of the aortic valve. Ultimately it may have ruptured into the left pleural cavity, a not unusual terminal event in the case of dissecting aneurysm. As I have said, however, in view of the findings which favor syphilis here, I do not see that dissecting aneurysm merits further consideration.

DR. ALEXANDER: Dr. Massie, did the electrocardiographic changes help in defining the terminal event?

DR. MASSIE: No, I do not think that they are of much aid. The change in rotation of the heart probably can be explained on the basis of accumulation of fluid in the left pleural cavity and prolongation of the QRS interval to progressive left ventricular dilatation. I do not think the tracings are consistent with the diagnosis of myocardial infarction. I suspect that the patient died of rupture of the aneurysm, and that the heart *per se* was not responsible for the terminal event.

DR. ALEXANDER: Do you think he had serious coronary artery disease?

DR. MASSIE: I am sure he had some, but it is well to point out that his coronary arteries were probably free of significant disease originally. Had they not been it is doubtful that the patient would have survived for such a long time with such a huge heart.

DR. ALEXANDER: Couldn't sudden death have occurred from occlusion of a coronary ostium?

DR. MASSIE: Yes, that is possible, and in that case electrocardiographic changes would not have had time to develop.

DR. I. JEROME FLANCE: Dr. Alexander, I have seen three patients with syphilitic aortic aneurysms which ruptured into the left pleural cavity. One patient lived for six months, one for three months and one died suddenly. In other words, this sequence of events is not incompatible with the course which this patient exhibited.

DR. ALEXANDER: In conclusion, I believe we would agree that this patient had syphilitic cardiovascular disease with a saccular aneurysm of the aorta, and aortic insufficiency probably due to syphilitic valvulitis of rather mild degree. The terminal event most likely was rupture of the aneurysm with bleeding into the left pleural space.

Clinical Diagnoses: Syphilitic cardiovascular disease with aneurysm of the aorta and syphilitic aortic valvulitis; rupture of syphilitic aneurysm with left hemothorax.

PATHOLOGIC DISCUSSION

DR. RUY PEREZ-TAMAYO. The left pleural cavity contained 4,000 cc. of fresh blood which compressed the left lung and displaced the mediastinal organs slightly to the right. The posterior part of the right pleural cavity was obliterated by numerous fibrous adhesions of the pleura to the chest wall. Immediately beyond the origin of the left subclavian artery from the aorta there was a saccular dilatation measuring 9 cm. by 7 cm. b 5 cm. which was loosely adherent to the inner aspect of the

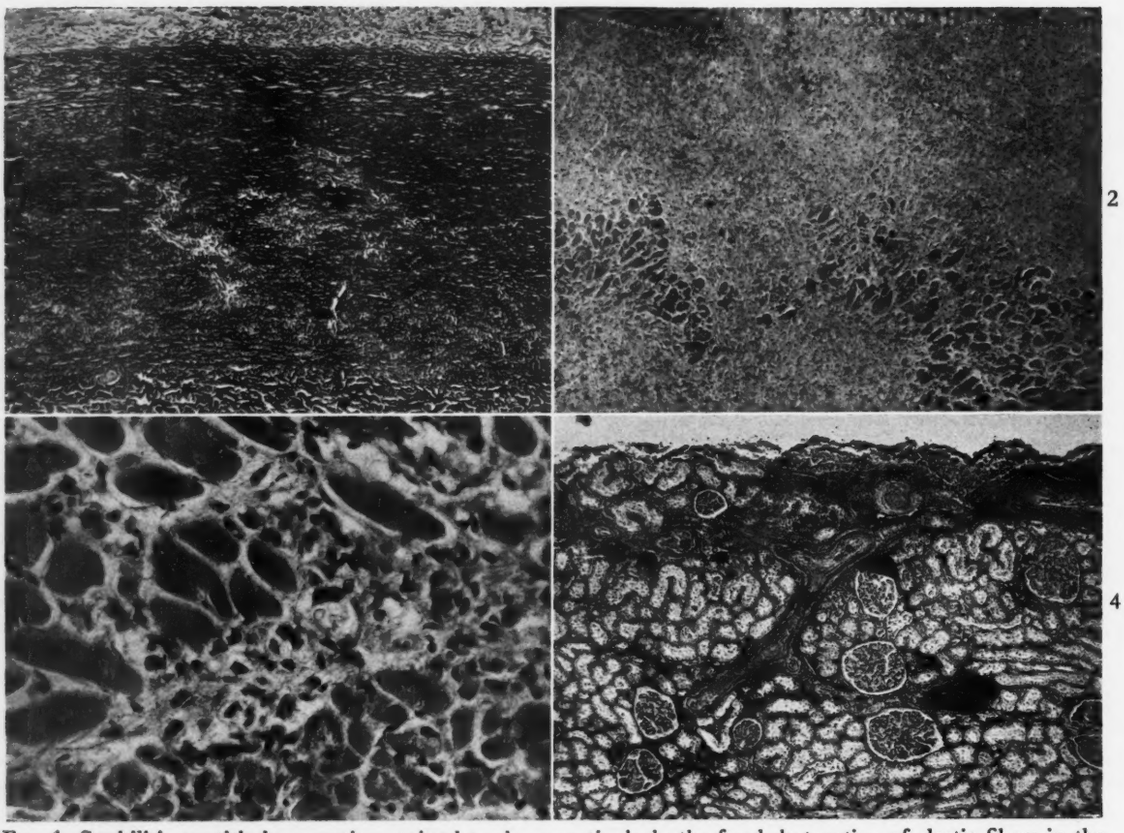

FIG. 1. Syphilitic aortitis in a section stained to show particularly the focal destruction of elastic fibers in the media.

FIG. 2. Focal fibrosis in the anterior wall of the left ventricle; the distribution and persistence of myocardial fibers suggested this lesion was coincidental to the hypertrophy of the myocardium rather than being related to syphilis.

FIG. 3. A microinfarct in the myocardium consisting of a few completely destroyed myocardial fibers and slight cellular reaction, probably due to the prolonged relative hypotension.

FIG. 4. Thickened vessels and a sclerotic glomerulus in the kidney indicating arteriolar nephrosclerosis although the tubules were generally well preserved and the cortical surface was grossly smooth.

superior portion of the upper lobe of the left lung. When dissected away from the lung, the aortic aneurysm showed on its lateral surface a perforation 2 cm. in diameter through which the contained laminated thrombus could be seen. The wall of the ascending aorta was dilated, and the intima was grey and wrinkled with longitudinal furrows and stellate depressions as well as many arteriosclerotic plaques. The aortic ring was not dilated and the cusps of the valve showed adhesions between the commissures and slight fibrous thickening but no rolling of the free edges in either direction. The endocardium of the left ventricle contained areas of focal thickening and a few petechiae. On the anterior aspect of the left ventricle there was a round whitish focus 2 cm. in diameter which on section penetrated into the myocardium without reaching the endocardium. The pattern of the myocardial fibers was not completely disrupted by this fibrosis. The abdominal aorta, as well as the coronary, cerebral, splenic, pancreatic, hepatic, renal and mesenteric arteries showed only a slight degree of arteriosclerosis. The liver was dark and congested. The kidneys each weighed 200 gm. and had smooth surfaces. No significant lesions were apparent in the other viscera.

DR. GUSTAVE J. DAMMIN: The appearance of the proximal aorta and the presence of an intrathoracic saccular aneurysm were typical of syphilitic aortitis, but the total lack of evidence of involvement of the aortic valve by the characteristic deformities of syphilis was unusual. Actually, the slight lesions that were present on that valve were those that have been suggested as possibly due to minimal rheumatic inflammation by some authorities. The aneurysm was located in the third portion of the arch of the aorta just distal to the origin of the left sub-

clavian artery. This is one of the less common sites of aortic aneurysm. According to some studies, about 50 per cent of all saccular aneurysms occur in the ascending portion, about 35 per cent in the transverse part of the arch and the remainder in the more distal portion of the aorta.

The immediate cause of death was bleeding from the ruptured aneurysm. From the appearance of the pleura and the surface of the aneurysm it seemed that several bouts of bleeding had occurred. There was slight organization of some fibrin on the pleural surface and the pleura of the left lung was adherent in part over the aneurysm. This finding suggested that at least one episode of bleeding had occurred before the terminal exsanguination and correlated with the clinical observation of rather sudden and severe decrease of erythrocytes and hemoglobin and appearance of fluid in the left pleural cavity.

Microscopically, the lesion in the aorta as shown by a stain for elastic tissue (Fig. 1) was a focal destruction of the elastic fibers in the media. There was an overlying fibrous plaque of the intima, and with other stains perivascular and focal infiltration of lymphocytes in the adventitia and media were prominent.

Figure 2 is an illustration of an area in the left ventricle recognized grossly as an area of fibrosis. The distribution of the fibrous tissue and the manner in which myocardial fibers were preserved in its interstices did not suggest a healed infarct as much as the type of rather diffuse fibrosis often seen in hypertrophied hearts. No recent infarct was grossly recognizable, but because of the suggestive ischemic changes in the electrocardiogram and the rather prolonged and profound depression of blood pressure it was suspected that microscopic foci of myocardial necrosis might be present. Two recent cases with similar histories of depression of previous hypertension and disseminated microinfarcts in the myocardium stimulated our interest, and in this case several small areas such as that in Figure 3 were found in the anterior portion of the left ventricle. They represented necrosis and destruction of just a few myocardial fibers and replacement by macrophages and young fibroblasts. The complete loss of the myocardial fibers suggested this lesion was between three to seven days in age.

One might consider the possibility of syphilis being responsible for the changes in the myocardium only to dismiss it. There is a type of syphilitic myocarditis that is well accepted. It is, however, related to the so-called acute phase of the disease and is an actual inflammation with accompanying focal necrosis rather than the primary necrosis seen in this case. That the fibrotic area in this heart could represent chronic syphilitic myocarditis seemed unlikely as the most recent and extensive anatomic studies of syphilis have cast doubt upon the very existence of any such pathologic entity.[4]

The final illustration (Fig. 4) is of a section of the kidney and shows this patient had moderately severe arterial and severe arteriolar nephrosclerosis and arteriolosclerosis commensurate with the history of hypertension and the hypertrophy of the heart. From our viewpoint this section was particularly interesting for the well preserved tubules. This finding was responsible for the smooth gross appearance of the cortical surfaces and furnished a rare and perplexing form of what might be termed smooth arteriolar nephrosclerosis.

In summary, the sequence of events in this patient's history can be reconstructed as cardiovascular renal disease with hypertension existing concomitantly with syphilitic aortitis for some period before the onset of the terminal events. It might be mentioned that such an association of marked hypertension with syphilitic aortitis is not uncommonly observed but no adequate explanation of a more than coincidental relationship is known. Sometime during this period a saccular aneurysm developed in the diseased aorta. The terminal course began with the first chest pain which was related to some leakage from the aneurysm into the mediastinal tissues and possibly into the left pleural cavity. There followed a drop in blood pressure and a period of relative hypotension responsible for the disseminated microinfarcts in the heart. Finally, the fatal episode consisted of complete rupture of the aneurysm and extensive hemorrhage into the left pleural cavity.

Final Anatomic Diagnoses: Syphilitic aortitis with an aneurysm in the descending aorta; rupture of the aortic aneurysm; arteriosclerosis of the aorta, moderate, and systemic arteries, slight; arteriolar nephrosclerosis; hypertrophy of the heart.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[4] ROSAHN, P. D. Autopsy studies in syphilis. *J. Ven. Dis. Inform., Suppl. No.* 21, Nov. 1, 1946.

Case Report

Chronic Disseminated Histoplasmosis*

An Investigation of Its Relationship to Sarcoidosis

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HISTOPLASMOSIS exhibits many similarities clinically and pathologically to tuberculosis and coccidiomycosis and, as has been repeatedly noted, may be mistaken for these diseases. It is not generally recognized that chronic disseminated histoplasmosis bears an equally striking resemblance to sarcoidosis, and that cases which satisfy the usual clinical, laboratory and histologic criteria for diagnosis of sarcoidosis may actually represent instances of histoplasmosis. Reimann and Price[1] reported a patient in whom the diagnosis of sarcoidosis had apparently been established by skin biopsy. When this patient was readmitted to the hospital four years later with severe laryngeal involvement, Histoplasma capsulatum was detected in granulomatous tissue secured by biopsy of the larynx. Death followed and necropsy demonstrated adrenal involvement. Review of the skin sections taken four years earlier revealed the presence of the organism which previously had been overlooked. Fatal histoplasmosis in young adults has been observed chiefly in association with tuberculosis, Hodgkin's disease or leukemia; Reimann and Price, therefore, suggested that sarcoidosis may have served as the primary disease upon which histoplasmosis supervened. It is also possible that histoplasmosis was the primary disease and simulated sarcoidosis.

Reported herewith is another case involving the problem of the relationship of these two diseases. The patient was extensively studied in an effort to ascertain whether the histoplasmosis represented an invasion of pre-existent sarcoidosis or whether histoplasmosis was responsible for the granulomatous lesions which were originally and still are typical of sarcoidosis. Also reported are the results of an investigation of twenty-two patients with sarcoidosis in whom histoplasmin skin tests, complement fixation and collodion agglutination tests for histoplasmosis, together with mycologic studies, have been performed in an effort to determine the frequency with which histoplasmosis may simulate or superinfect sarcoidosis.

CASE REPORT

R. A., a thirty-six year old white male Red Cross worker, was first admitted to the Valley Forge Army Hospital in 1948 because of sore throat and hoarseness. Born in Cleveland in 1912, he had resided in Ohio until 1942. Symptoms of cough and chest pain developed in June, 1942, while en route to the Southwest Pacific on a transport. These symptoms subsided but recurred later in 1942 when x-ray examination of the chest, his first since a negative survey film in 1938, showed areas of infiltration. Study while hospitalized in Fiji revealed no other abnormalities and he was returned to duty. Subsequent x-ray examinations showed no change until December, 1943, when an increase was noted; the patient was again hospitalized, further studied and returned to duty. In 1944 he was returned to the United States and admitted to Walter Reed General Hospital at which time a tuberculin test was negative, and sarcoidosis was suspected. He was again returned to duty subsequently feeling entirely well. In 1946 he attended the University of Pennsylvania and in January, 1947, he visited the Henry Phipps Institute of the University of Pennsylvania for his regular semi-annual x-ray examination. The patient was thoroughly studied at this time despite the absence of symptoms. Physical examination was negative except for slightly enlarged lymph nodes in the right side of the

* From the Valley Forge Army Hospital, The Woman's Medical College of Pennsylvania, the Graduate School of Medicine and the Departments of Dermatology and Microbiology, School of Medicine, University of Pennsylvania. This study was aided by a research grant from the National Institutes of Health, Public Health Service.

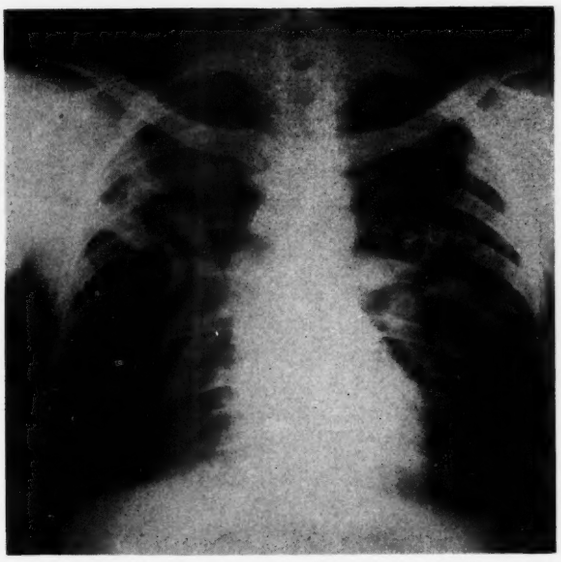

FIG. 1. Chest roentgenogram, January 11, 1947, showing moderately dense bilateral pulmonary infiltration.

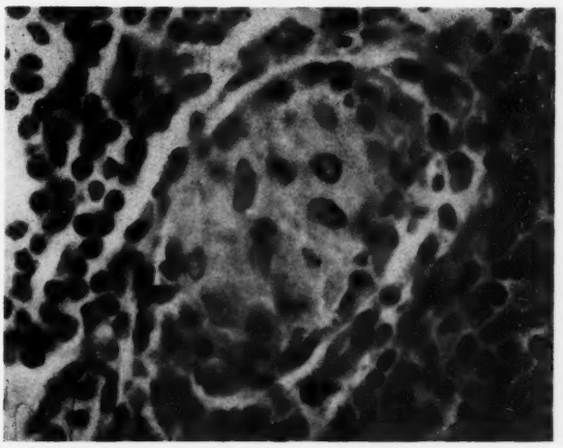

FIG. 2 Section of cervical lymph node, excised February 14, 1947, showing epithelioid tubercle; × 400.

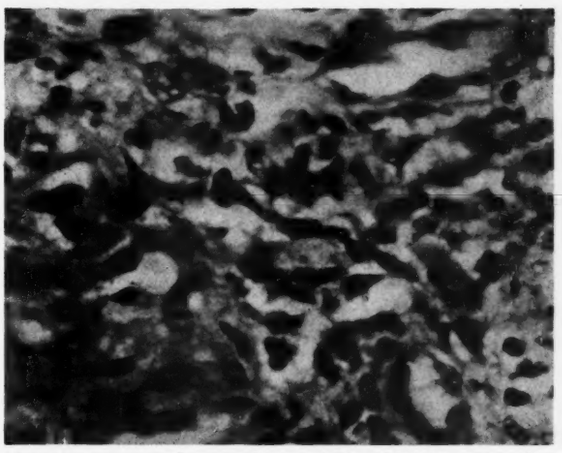

FIG. 3. Laryngeal granuloma, stained by hematoxylin and eosin; × 400.

neck and in the left axilla. His weight was 165 pounds. A tuberculin test was negative, blood count and sedimentation rates were normal. X-ray examination showed moderately dense nodular infiltration through both lung fields. (Fig. 1.) Electrophoretic analysis of the serum proteins showed increased alpha-2 and gamma globulins. A cervical lymph node was excised and showed large epithelioid tubercles indicative of sarcoidosis. (Fig. 2.)

The patient was well during the ensuing year except for an attack of grippe which resulted in a weight loss of 10 pounds. In January, 1948, in Dayton, Ohio, he contracted a sore throat which persisted for several months in spite of local therapy and administration of sulfonamides and penicillin. In September, 1948, he was assigned to Valley Forge Army Hospital. Shortly thereafter he noted hoarseness which rapidly became severe. In November laryngeal examination revealed marked edema of the left arytenoid and aryepiglottic fold. The left vocal cord could not be seen, but the right cord and ventricular band were edematous and ulcerated. Chest x-ray examination showed no significant change from the appearance in the films of 1947.

The development of laryngeal involvement in a patient with a diagnosis of sarcoidosis suggested the possibility of histoplasmosis. A skin test with histoplasmin was positive (1 +) and a biopsy of the subglottic mass was secured. The sections were reported to show a non-specific granuloma (Fig. 3); no evidence of histoplasmosis was detected. Cultures for fungi were reported negative and inoculated guinea pigs showed no evidence of tuberculosis. In February, 1949, a mycologic laboratory was organized at the Valley Forge Army Hospital. The biopsy sections were reviewed and occasional intracellular budding cells were recognized. Another laryngeal biopsy on March 1, 1949, demonstrated numerous large reticulo-endothelial cells containing typical Histoplasma capsulatum. (Fig. 4.) A rapid increase in symptoms occurred. There was almost complete aphonia, malaise and anorexia developed and there was a weight loss of fifteen pounds. On March 16, 1949, the patient was hospitalized. He was thin and chronically ill and had fever of 100°F. Dyspnea was noted on slight effort. There was pallor but no cyanosis. Two sharply punched out ulcers 2 cm. in diameter had appeared on the soft

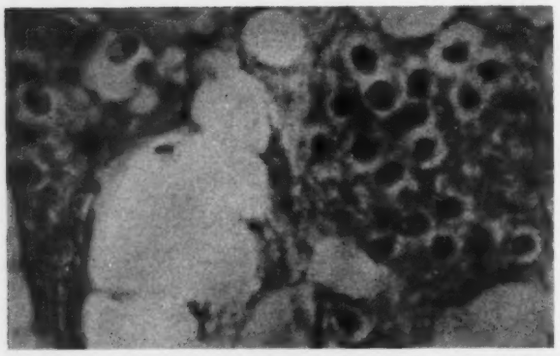

FIG. 4. Laryngeal granuloma, stained by Hotchkiss-McManus technic, showing Histoplasma capsulatum; × 930.

palate since his last examination. Laryngoscopy showed no change from the examination on November, 1948. There was slight bilateral cervical lymph node enlargement. The remainder of the physical examination was negative. X-ray examination of the chest showed little change. X-rays of the hands and feet and a flat plate of the abdomen were negative.

Laboratory findings included a normal urinalysis and blood count. The sedimentation rate (Wintrobe) was 34 mm. Serologic tests for histoplasmosis were positive. (Table 1.) Cultures of Histoplasma capsulatum were obtained from the palatal ulcerations, from a third laryngeal biopsy and from sputum. No growth was obtained from aspirated sternal marrow.

A cervical lymph node biopsy revealed almost complete replacement of glandular structure by tubercles; the sections were compared with those secured in the lymph node biopsy performed in 1947. Careful search failed to demonstrate histoplasma in either tissue specimen and both specimens appeared typical of sarcoidosis. Culture of a portion of the lymph node was negative for histoplasma.

Electrophoretic study of the serum proteins showed a hyperglobulinemia of 5.6 gm. per cent with marked elevation of the alpha-2 and gamma fractions.

The hospital course was as follows: The patient became afebrile within one week. Strict bed rest was maintained and voice rest was practiced. A course of penicillin had no apparent effect upon the pharyngeal ulcers or upon the patient's general condition. On the basis of a report that streptomycin was the most effective of the commercially available antibiotics against histoplasma,[3] this drug was given in doses of 0.5 gm. twice daily for forty-two days. Although the patient's weight increased from 140 to 147 pounds and the pharyngeal and laryngeal lesions showed marked improvement, cultures remained positive in June and up to July 19th. Cultures taken July 26th and August 2nd were negative. On August 3, 1949, before the report of the last two cultures was available, treatment with bacillomycin B[3] was instituted in dosage of 50 mg. every six hours. Local and systemic reactions were extremely severe and after a week forced discontinuance of treatment. Twelve days later treatment was resumed employing 50 mg. doses every twelve hours and was continued for nine days. A total of 2.5 gm. of bacillomycin* was given. During the period of administration the patient lost 12 pounds and experienced agonizing pain from the local reactions.

TABLE 1

SEROLOGIC TESTS FOR HISTOPLASMOSIS
PATIENT R. A.

	3/28/49	6/14/49	8/26/49	3/4/50	7/13/50	3/27/51
Complement fixation	1:10	1:10	1:10	1:20	1:80	1:40
Collodion agglutination	1:80	1:80	1:60	1:80	1:80	1:80

At the time of discharge from the hospital, September 27, 1949, the patient had regained his lost weight, weighing 149 pounds; the palatal ulcers were almost healed. Laryngeal examination showed some reduction in the arytenoid swelling and no ulceration was present. The sedimentation rate remained elevated and x-ray examination of the chest showed contraction and clearing of the infiltration. Following discharge no change was observed in the patient's condition except for the de-

* Supplied through the courtesy of Dr. Joseph Seifter, Wyeth Institute of Applied Biochemistry.

velopment of an indolent ulcer of the left nostril. He was given atabrine 1.0 gm. daily for sixty days because of a report that this drug had been beneficial in experimental histoplasmosis.[4] Following an acute respiratory infection in March, 1950, loss of weight and increasing dyspnea on effort were noted and in May stridor and difficult breathing at rest occurred.

On his second hospital admission the patient was admitted to the Woman's Medical College Hospital on July 10, 1950. His weight was 129 pounds and the patient appeared chronically ill. Respirations were somewhat labored and the patient was able to speak only in a whisper. Physical examination revealed little change from the findings noted on the previous hospitalization. There was questionable pigmentation of the face and the blood pressure was 100/60. An ulcer 1 cm. in diameter was present in the left nasal vestibule. The palatal ulcerations had healed. Laryngeal examination showed tremendous enlargement of the arytenoids so that only a minimal airway was present. There was, as before, a negative tuberculin test, positive histoplasmin test, positive serologic tests for histoplasmosis, and hyperglobulinemia. X-ray examination of the chest showed no change from films of September, 1949. (Fig. 5.) Biopsies of a cervical lymph node and the nasal ulcer showed epithelioid tubercles typical of sarcoidosis. Cultures for histoplasma were negative.

Detailed endocrinologic study was carried out in an effort to detect adrenal involvement. No reduction in eosinophils occurred in the Thorn test employing epinephrine. The Kepler-Power index was 19. Excretion of 17-ketosteroids was reduced to 6.9 mg. in twenty-four hours (normal 12 mg.) and the glucose tolerance curve was flat. Urinary gonadotropins and corticoids were within normal limits. In view of the evidence of impaired adrenal function, a course of cortisone, 100 mg. twice a day for ten days, was given. No improvement was observed except for transient and slight reduction in size of the arytenoids and nasal ulcer. The patient was discharged on August 4, 1950, but difficulty in respiration recurred with increased severity and on August 10th the patient was readmitted to the Woman's Medical College Hospital and a tracheotomy was performed, with marked increase in comfort.

Following discharge on August 24th there was steady improvement in the patient's general condition. Weight had increased to 140 pounds by March 15, 1951, and the patient's voice, with

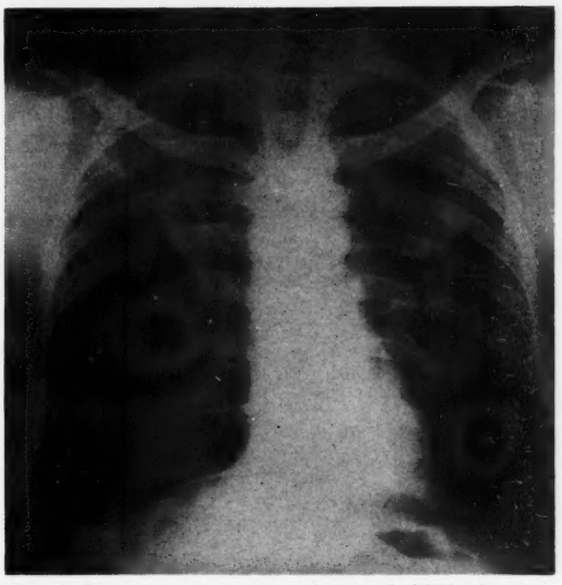

FIG. 5. Chest roentgenogram, August 5, 1950, showing partial clearing and contraction of the infiltration.

tracheotomy, was better than it had been for two years. Repeated punch biopsies of the arytenoid were successful in increasing the airway. Histologic study revealed dense fibrosis, with scattered epithelioid tubercles. Occasional budding histoplasma cells were noted but cultural studies were consistently negative.

Repetition of the endocrinologic studies in March, 1951, revealed a normal water excretion test and glucose tolerance curve. Eosinophils fell from 337 to 200 after infusion of epinephrine. Urinary excretion of 17-ketosteroids was 8.2 mg. The improvement in these tests suggested that the impaired function observed in studies carried out in July, 1950, was not due to adrenal involvement by histoplasmosis but was probably in large measure the result of chronic disease and anoxemia. A major factor in the improvement appeared to have been the correction of the anoxia by tracheotomy.

Summary. A white male, native of Ohio, first developed respiratory symptoms in 1942 at the age of thirty. X-ray examination demonstrated bilateral pulmonary infiltration. A diagnosis of sarcoidosis was made in 1947 on the basis of a cervical lymph node biopsy, negative tuberculin test and hyperglobulinemia. There was no significant impairment of health until 1948 when sore throat and hoarseness developed. Edema and ulceration of the larynx were found and laryngeal biopsy resulted in detection of histoplasma. Cultures of Histoplasma capsulatum

were thereafter obtained from the larynx, pharyngeal ulcers and sputum. Repetition of cervical lymph node biopsy showed typical sarcoidosis; histoplasma could not be demonstrated. Treatment consisting of six months' bed rest and courses of streptomycin and bacillomycin resulted in clinical improvement, and histoplasma organisms were no longer demonstrable on culture. In 1950 laryngeal obstruction became more marked but a tracheotomy resulted in marked clinical improvement. A course of cortisone therapy was given with no apparent effect.

Biopsy sections secured in twelve patients were stained by the Hotchkiss-McManus technic[6] and reviewed for histoplasma organisms. None was found. In five other patients cultural studies of excised tissue specimens were negative.

TABLE II

RESULTS OF STUDIES FOR HISTOPLASMOSIS IN PATIENTS WITH SARCOIDOSIS

	Histoplasmin (1-10) Skin Test	Complement Fixation	Collodion Agglutination	Mycologic Examination
Positive	4	0	1	0
Negative	18	19	18	17
Total	22	19	19	17

SURVEY STUDY

A study was undertaken to detect possible evidence of histoplasmosis in twenty-two other patients considered to have sarcoidosis on the basis of clinical, laboratory and biopsy evidence.

The histoplasmin skin test was performed in all twenty-two patients (Table II) employing test dilutions of 1:100 and 1:10. The histoplasmin was supplied by Dr. Joseph D. Aronson of the Henry Phipps Institute, with potency established in control studies. Positive reactions were noted in four patients, 17.4 per cent. This frequency is less than that observed in a group of twenty-nine controls of whom 45.0 per cent reacted to 1:10 histoplasmin.

Serologic studies, comprising complement fixation and collodion agglutination tests,[5] were carried out on sera from nineteen patients. All were negative except for one patient who had negative complement fixation test but a 4+ collodion agglutination test in titer of 1:10. Although this was considered a suspicious reaction, the patient's histoplasmin skin test was negative and detailed clinical and laboratory study failed to afford other evidence of histoplasmosis.

COMMENT

Histoplasmosis was first recognized as an almost invariably fatal infection. Parsons and Zafaronetis' thorough review[7] in 1945 summarized the seventy-one cases in which the diagnosis of histoplasmosis had been established; all but four were known to have died and three of the survivors had ulcers of the tongue as the only manifestation of the disease. Since 1945 it has been demonstrated that infection with Histoplasma capsulatum is relatively common and widespread in the United States and is, with few exceptions, subclinical and benign. The clinical and laboratory features of histoplasmosis are best described by distinguishing four principal types of the disease.

Active Primary Histoplasmosis. Detection of cases in the acute phase of primary histoplasmosis has proved unexpectedly difficult despite the fact that epidemiologic studies employing the histoplasmin skin test have demonstrated infection in 75.9 per cent of college students from southwestern Ohio[8] and in 78 per cent of student nurses tested in Missouri.[9] A nineteen year old white soldier recently observed by us had developed symptoms of grippe two months after transfer to a post in Kentucky. The symptoms subsided the day following hospitalization but a routine chest x-ray disclosed in the upper right lobe a small area of pneumonitis which resolved in a few days leaving a thin-walled cavity 2 cm. in diameter. Two weeks later the cavity had disappeared leaving at the site a faintly visible nodule. This sequence is characteristic of primary coccidiomycosis, but negative coccid-

ioidin and tuberculin tests, a positive histoplasmin reaction and the development of strongly positive serologic tests indicate that the lesion probably represented a primary histoplasmosis. An illness so slight and brief would ordinarily in civilian life have led neither to hospitalization nor x-ray examination. It is evident that the primary infection of histoplasmosis, like that of tuberculosis and coccidiomycosis, is in most cases responsible for few symptoms.

A similar instance, in a forty-one year old female, of apparent primary infection in which histoplasma were demonstrated by sputum culture has been reported by Bunnell and Furculow[10] who also detected several instances in children of primary histoplasmosis exhibiting rapid resolution and eventual calcium deposition. Other benign cases in children with isolation of the organism by blood culture[11,12] have recently been reported. A transient sharp rise in serologic titer was observed in all of these cases and histoplasmin skin tests were positive.

Healed Primary Histoplasmosis. Although the ephemeral acute phase has been detected infrequently, the calcific residuals which represent healed primary histoplasmosis have been found to be common. In the endemic areas of the middle West histoplasmosis appears to be far more often the cause of pulmonary calcifications than tuberculosis.[13] Serologic and cultural studies in this stage of the disease are negative and the calcifications have little clinical significance.

Acute Disseminated Histoplasmosis. This form, usually rapidly fatal, is characterized by involvement of the tongue, pharynx, larynx, adrenals, liver and spleen as well as the lungs. These patients, especially in the terminal phase, are anergic and fail to react to histoplasmin. Histoplasma may occasionally be demonstrable by culture of aspirated marrow. This form of the disease occurs usually in infants or the aged, or in those debilitated by an underlying disease such as tuberculosis or neoplasma.

TABLE III

Author	Year of Diagnosis	Age	Sex	Race	Organs Involved	Outcome
Mantell [13]	1938	--	M	W	Lymph nodes, liver spleen	1942: well and working
Miller [14]	1938	32	M	W	Cervical lymph node	1944: died of histoplasmosis and Hodgkin's disease
Simson [15]	1941	55	M	W	Tongue, lips	1942: unimproved
Weed [17]	1943	23	M	W	Oropharnyx, lungs	1944: died of histoplasmosis
Furculow [18]	1943	64	M	W	Lungs, spleen, adrenals	1949: died of histoplasmosis
Reimann [1]	1944	31	F	N	Lungs, skin	1948: died of generalized histoplasmosis
Curtis [18]	1944	42	M	W	Tongue, skin, nares	1945: improved
Stuart [19]	1947	24	M	W	Lungs, pleura	1948: recovered
Lejeune [20]	1947	44	M	W	Larynx	1950: larynx normal, ill with Addison's disease
Furculow [17]	1947	52	M	W	Lungs (bilateral cavitation)	1950: alive but worse
Furculow [17]	1949	64	M	W	Lungs, larynx	1950: improved

Chronic Disseminated Histoplasmosis. A number of instances of systemic histoplasmosis exhibiting a chronic course have been reported. In many the disease ultimately proved fatal but in others marked improvement occurred, with apparent arrest of the disease in some instances. Table III lists reported patients with disseminated histoplasmosis who lived for at least a year after the diagnosis was proven. Omitted from this table are patients, such as those reported by Riley and Watson,[21] and Hansmann and Schenken,[22] whose history suggests disease of long standing before the diagnosis was established by demonstration of histoplasma. The organs principally involved in chronic histoplasmosis are the larynx, lungs, lymph nodes and oral structures. Skin tests, serologic studies and cultures are usually positive. Chronic histoplasmosis clinically local-

ized to the lungs[23] or genitalia[18] has been reported. Such cases appear to have a relatively good prognosis. Possibly, these cases represent local invasion from the sites of primary infection but they may represent isolated manifestations of a systemic infection.

The parallelism between histoplasmosis and coccidiomycosis is remarkable. Both diseases were originally recognized as rare and invariably fatal infections, and both have been shown to be widespread infections usually subclinical and benign. Disseminated coccidiomycosis has been estimated by Smith and his associates[24] to occur once in every 380 white persons infected. Data on the frequency of disseminated histoplasmosis are insufficient to permit calculation of such a rate but it is probably even lower than in coccidiomycosis. However, in this country a very much larger number of persons have been infected with histoplasma than with coccidioides and disseminated histoplasmosis is therefore not a rarity. One point of difference between these two fungal diseases is worthy of emphasis because of its clinical importance. Coccidioidal infection, with rare exceptions, is acquired only in the desert areas of the southwestern states, and this diagnosis receives little consideration in persons who have not resided in or visited these states. Histoplasmosis, on the other hand, is most prevalent in the Missouri, Tennessee and Ohio river valleys, but infection can apparently be acquired anywhere in this country and absence of residence in the endemic areas does not exclude the possibility of this disease.

It is with chronic disseminated histoplasmosis that sarcoidosis may be confused, clinically as well as pathologically. In a patient with diffuse pulmonary disease, a negative tuberculin test and hyperglobulinemia, the description by a competent pathologist of epithelioid tubercles in an excised lymph node would ordinarily be considered to have proven the diagnosis of sarcoidosis. The histologic appearance of histoplasmosis resembles that of sarcoidosis so much that it is essential for the pathologist to employ newer staining methods[6] in search for histoplasma in all sarcoid as well as in other tuberculoid and granulomatous lesions. Failure to recognize the budding cells led to an erroneous diagnosis in the patient described by Reimann and Price.[1] In another case known to us, which had been reported as an instance of sarcoidosis of the adrenals, a review of the sections made because of the known predilection of histoplasmosis to involve the adrenals resulted in the demonstration of typical fungus cells.[25]

It is not to be inferred that a large proportion of cases of sarcoidosis are due to histoplasmosis. Epidemiologic studies indicate that the majority of patients with sarcoidosis are natives of the South Atlantic states, an area in which the prevalence of histoplasmosis is considerably less than in the central states. The failure to find evidence of histoplasmosis in twenty-two random patients with sarcoidosis in the Philadelphia area indicates that in the majority of patients with this disease another etiology must be sought. The demonstration that histoplasmosis can produce granulomatous lesions resembling those of sarcoidosis, as well as epidemiologic evidence[26,27] demonstrating a rural or agricultural background in most patients with sarcoidosis, warrants continued interest in the possibility that sarcoidosis is a disease of mycotic etiology, even though efforts to detect fungi have thus far been fruitless.

It has not been possible to establish whether the patient herein described originally had sarcoidosis and subsequently developed histoplasmosis or whether disseminated histoplasmosis simulated sarcoidosis. The latter explanation is supported by certain epidemiologic and anatomical evidence. The patient was a white native of Ohio although of sixty patients with sarcoidosis studied by us in Philadelphia only three were northern born whites.[28] The distribution of lesions was unusual for sarcoidosis. The hilar nodes, eyes, lacrimal and parotid glands, skin and bones which are frequently involved in sarcoidosis were spared. Although mucosal infiltration of the larynx is not uncommon, only four instances of destructive laryngeal lesions in sarcoidosis have been reported[29–32] and none of these patients was studied to exclude histoplasmosis. Similarly, adrenal damage is rare in sarcoidosis[33] and common in histoplasmosis. In July, 1950, prior to tracheotomy, rather marked adrenal impairment was indicated by the abnormal water excretion test, epinephrine eosinophil response and glucose tolerance curve and the diminished excretion of 17-ketosteroids. The more normal values observed on repetition of these tests in March, 1951, however, suggests that the adrenal insufficiency previously present was at least in part the result of chronic anoxia and toxemia. Although it has not been possible to establish

whether in this patient histoplasmosis simulated or superinfected sarcoidosis, it appears clear that the association of these two relatively uncommon diseases is not merely coincidental. A search for histoplasmosis by means of the skin test, serologic study, cultural methods and the Hotchkiss-McManus staining technic is especially indicated in patients with apparent sarcoidosis who come from the Ohio, Tennessee or Missouri valleys, or who have oral, laryngeal or adrenal involvement.

No specific therapy is available for histoplasmosis. Streptomycin,[3] bacillomycin B[4] and atabrine[5] have been reported fungicidal *in vitro;* the clinical improvement shown by the patient reported did not appear directly related to use of these drugs and was more probably due to bed rest and high protein diet. Noteworthy improvement also appeared to follow the correction of laryngeal obstruction by tracheotomy.

SUMMARY AND CONCLUSIONS

1. Disseminated histoplasmosis exhibiting a chronic course is being recognized with increased frequency.

2. The histologic appearance of histoplasmosis resembles that of sarcoidosis and cases which satisfy the usual clinical, laboratory and pathologic criteria of the latter disease may occasionally represent instances of chronic histoplasmosis.

3. A case is reported in which disseminated histoplasmosis was demonstrated in a patient who had typical clinical, laboratory and biopsy findings of sarcoidosis. Extensive study failed to establish whether the histoplasmosis represented an invasion of pre-existent sarcoidosis or whether the histoplasmosis was responsible for the granulomatous lesions which simulated sarcoidosis.

4. Histoplasmosis infrequently is a factor in patients with sarcoidosis studied in Philadelphia. Application of skin tests, serologic tests and mycologic studies to a group of twenty-two such patients failed to demonstrate evidence of histoplasmosis.

5. The diagnosis of sarcoidosis should be made only by exclusion. Tuberculosis and beryllium granulomatosis as well as histoplasmosis may simulate sarcoidosis and must be excluded by appropriate studies before the diagnosis of sarcoidosis is warranted. Special search should be made for histoplasma in patients with apparent sarcoidosis who have resided in the Missouri, Tennessee or Ohio valleys and who have oral, laryngeal or adrenal involvement.

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**J.A.M.A. 146:35, 1951.*

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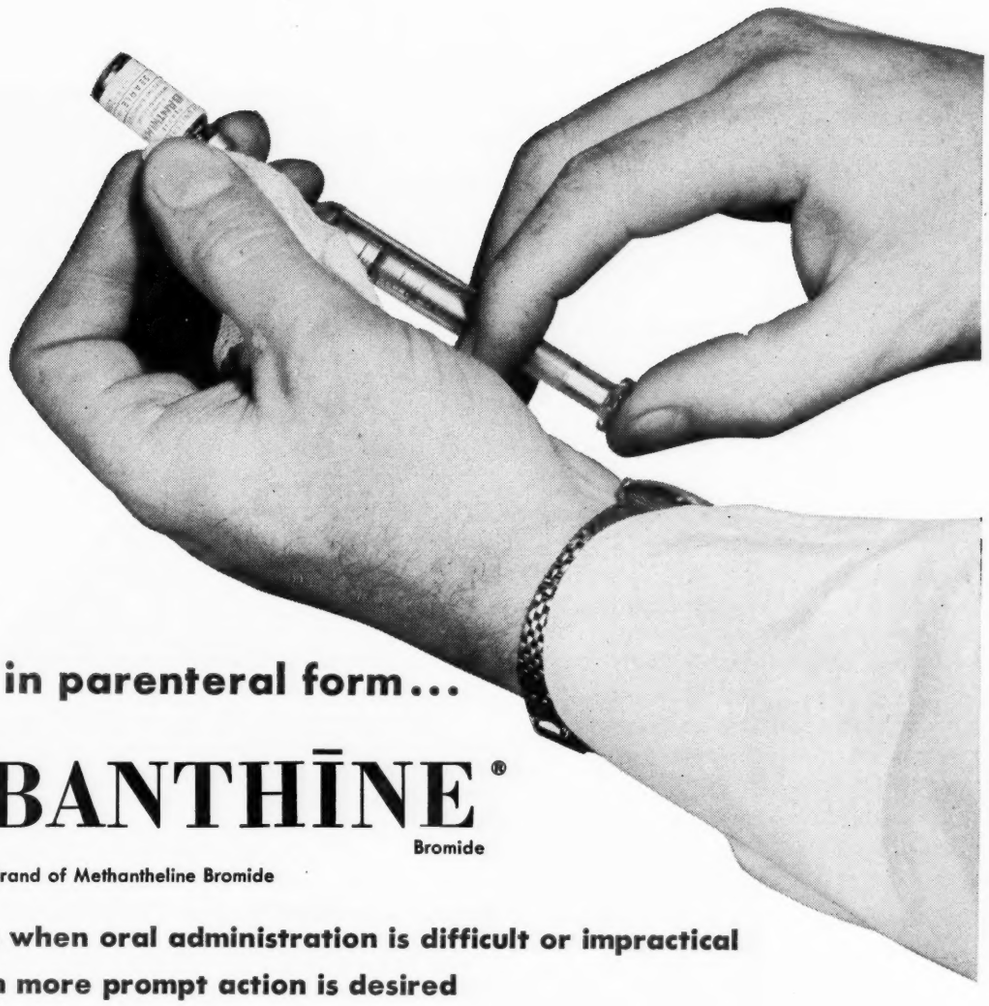

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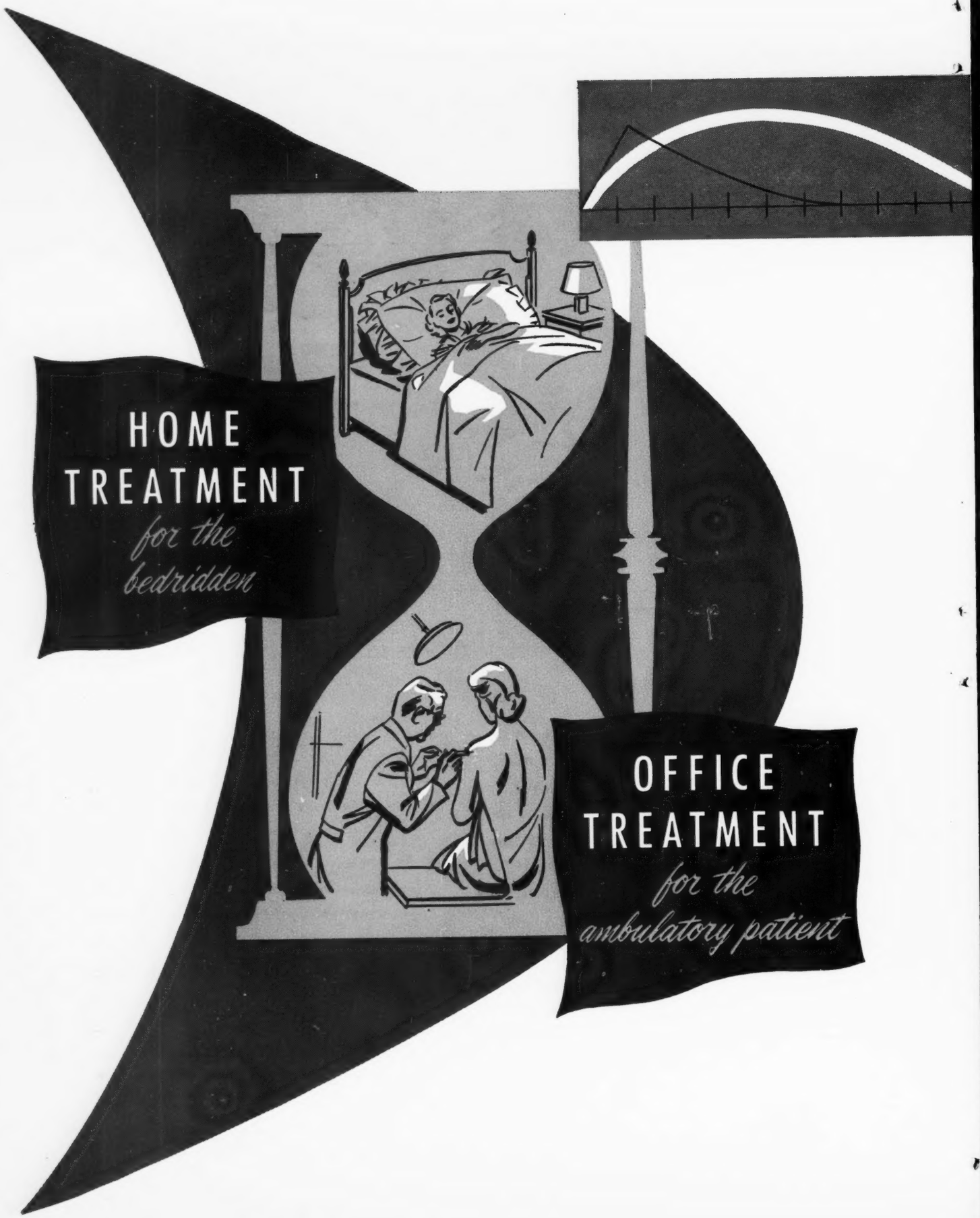
HOME
TREATMENT
for the
bedridden
OFFICE
TREATMENT
for the
ambulatory patient

ACTHAR* *Gel* IS LONG-ACTING

ACTHAR *Gel*—the new LONG-ACTING repository preparation—simplifies ACTH therapy comparable to the management of diabetes with long-acting insulin. Home or office treatments become readily applicable with substantial economy to the patient. Greatly prolonged therapeutic action and convenience of administration are distinct advantages of ACTHAR *Gel*.

Recent clinical studies have firmly established the recommended dosage of ACTHAR *Gel*. Established dosage for optimum therapeutic effects is important in the everyday use of ACTH in your practice.

Indications: Rheumatoid arthritis, rheumatic fever, acute lupus erythematosus, drug sensitivities, severe bronchial asthma, contact dermatitis, most acute inflammatory diseases of the eye, acute pemphigus, exfoliative dermatitis, ulcerative colitis, acute gouty arthritis, secondary adrenal cortical hypofunction. **Supplied:** 5 cc. multiple dose vial containing 20 I.U. per cc., and 5 cc. multiple dose vial containing 40 I.U. per cc.

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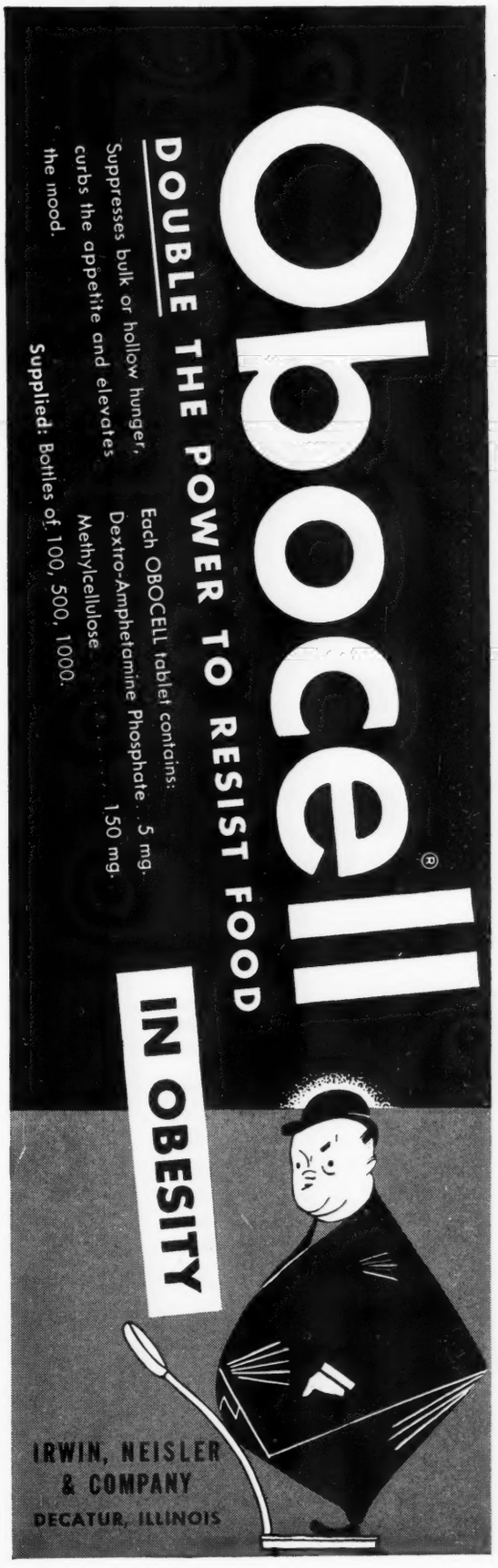
PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH



Meat Helps Make Americans the World's Best Nourished People

Recent estimates of the U. S. Department of Agriculture show that the per capita consumption of meat in the United States approaches seven ounces per day. How effectively this average amount of meat in the daily diet contributes to making Americans the world's best nourished people is indicated by the following data. The figures give the average amounts of protein, iron, phosphorus, niacin, riboflavin, and thiamine provided by six-ounce servings of cooked meat (averages of the amounts furnished by six ounces each of cooked beef, lamb, pork, and veal)* and their percentages of the daily dietary allowances recommended by the National Research Council for a sedentary man (154 lb.).

	Amounts per 6 oz.† of Average Cooked Meat	Percentages of Recommended Daily Dietary Allowances
Protein (Biologically complete)	44 Gm.	63%
Iron	5.6 mg.	47%
Phosphorus	414 mg.	28%
Niacin	9.5 mg.	79%
Riboflavin	0.44 mg.	24%
Thiamine	0.50 mg.	42%

† 7 oz. of fresh meat, when cooked, weigh approximately 6 oz.

The important nutrients of meat, however, are not limited to those given above, for which the amounts needed for adequate nutrition have been established. Other nutrients provided by meat, but for which daily needs have not yet been established, include other members of the B complex—biotin, choline, folic acid, inositol, pantothenic acid, pyridoxine, and vitamin B_{12}—and many minerals essential in nutrition.

Every cut and kind of meat supplies these many nutrients for promoting health and efficiency in adults, and for health and good growth and development in children. Besides, meat is rapidly and almost completely digested, and its extractives stimulate the flow of gastric juice. Hence there is sound justification—nutritional, physiologic, and psychologic—for meat being a favorite food in the diet of the American people and in special diets prescribed by the physician.

---

*Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, Agriculture Handbook No. 8, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, 1950.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago... Members Throughout the United States

IN HYPERTENSIVE CRISES

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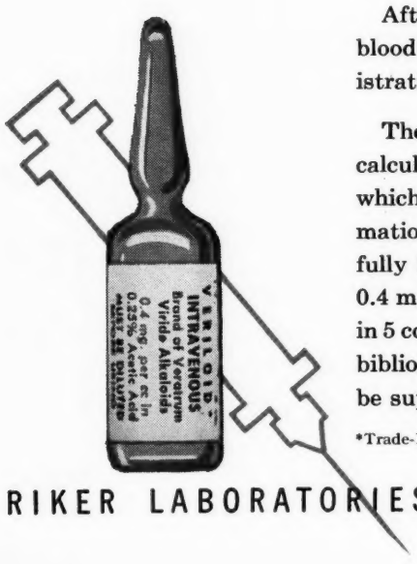
SOLUTION

VERILOID INTRAVENOUS*

A valuable emergency drug for controllable, immediate, and substantial reduction of the arterial tension.

A MUST IN EVERY EMERGENCY BAG



Solution Veriloid Intravenous is an important new emergency drug. For the first time it makes available a purified fraction of Veratrum viride, generically designated alkavervir, which can be given by vein. This powerful hypotensive agent is capable of dropping the blood pressure within a matter of minutes in a majority of patients. It makes possible immediate control of the arterial tension in the conditions in which a continued hypertensive state could readily lead to serious complications or even to death. Thus it finds valuable application in the emergency treatment of hypertensive states accompanying cerebral vascular disease, malignant hypertension, and hypertensive crisis (encephalopathy).

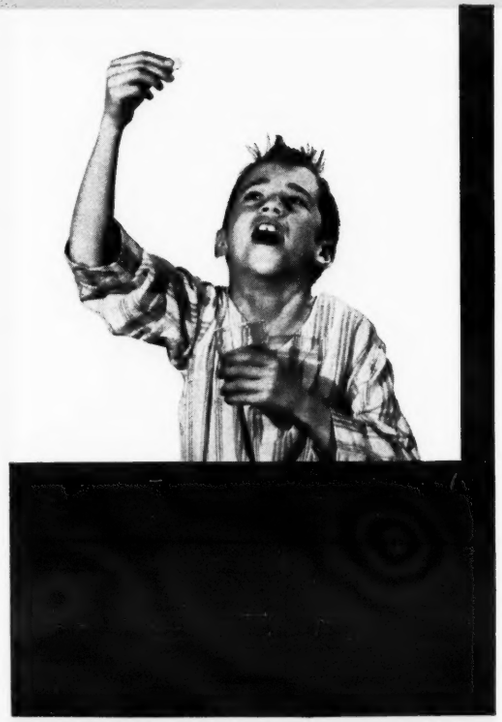
After a satisfactory drop in tension has been achieved, the blood pressure can be controlled subsequently by the administration of suitable oral medication.

The dosage of Solution Veriloid Intravenous must be carefully calculated, and the injection must be given slowly. The leaflet which accompanies the ampules contains comprehensive information on dosage and administration and should be read carefully before therapy is initiated. Solution Veriloid Intravenous, 0.4 mg. of Veriloid standard reference powder per cc., is supplied in 5 cc. and 20 cc. ampules. Detailed literature and comprehensive bibliography on this product of Riker Laboratories research will be supplied promptly on request.

*Trade-Mark of Riker Laboratories, Inc.

RIKER LABORATORIES, INC. 8480 BEVERLY BLVD. • LOS ANGELES 48, CALIF.

simplifies antibacterial dosage

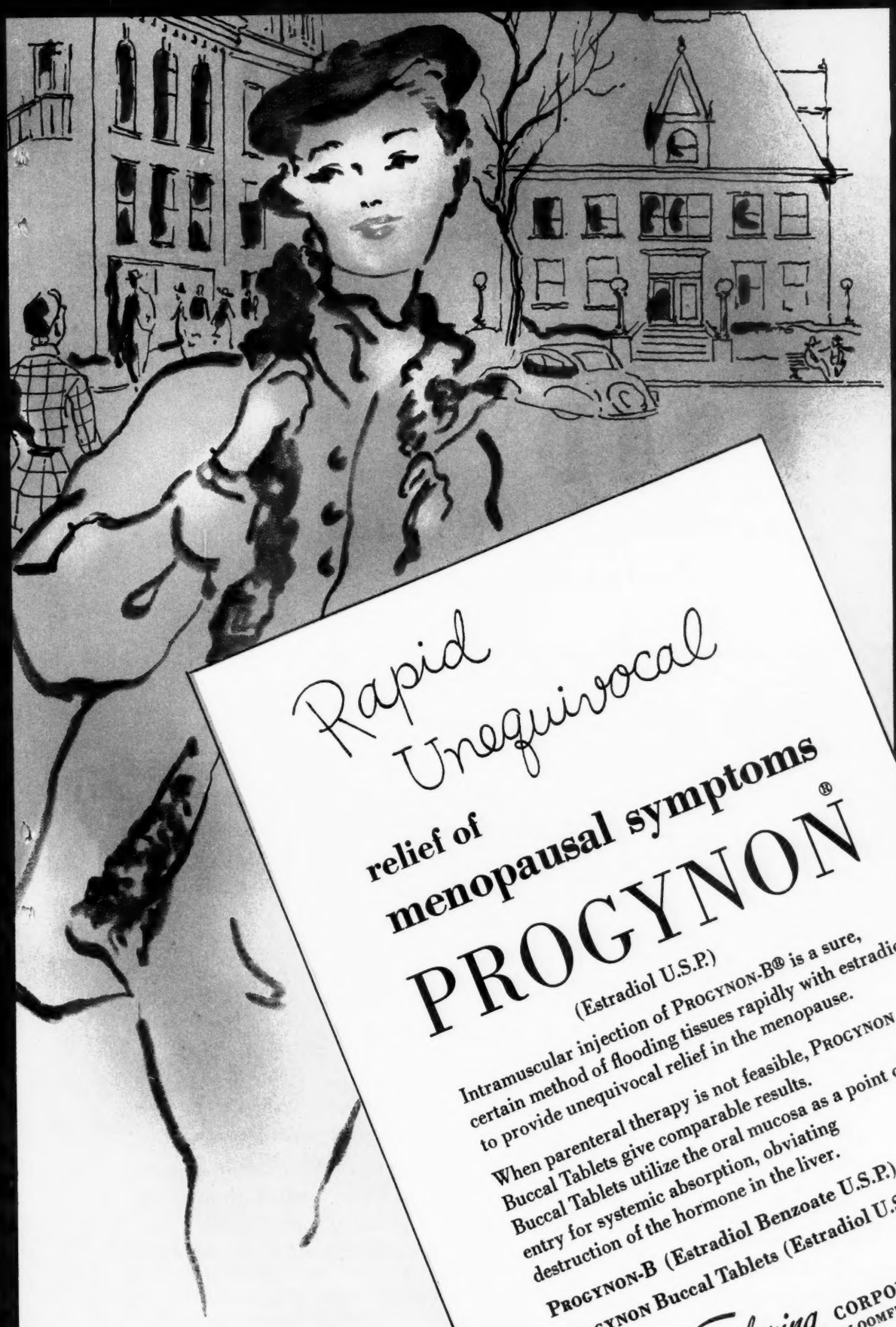


This triple-sulfonamide, high-potency-penicillin preparation simplifies treatment (only 4 doses daily in many cases), provides sustained bacteriostasis in a wider bacterial spectrum. In some instances, treatment may be shortened with less cost to the patient. Bottles of 60 compressed tablets (slotted). Sharp & Dohme, Philadelphia 1, Pa.

Sharp & Dohme

Pentresamide®-250

Triple sulfonamide with penicillin (250,000 units)



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Unequivocal

relief of
menopausal symptoms

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(Estradiol U.S.P.)

Intramuscular injection of PROGYNON-B® is a sure, certain method of flooding tissues rapidly with estradiol to provide unequivocal relief in the menopause.

When parenteral therapy is not feasible, PROGYNON Buccal Tablets give comparable results. Buccal Tablets utilize the oral mucosa as a point of entry for systemic absorption, obviating destruction of the hormone in the liver.

PROGYNON-B (Estradiol Benzoate U.S.P.)
PROGYNON Buccal Tablets (Estradiol U.S.P.)

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FOR YOUR CARDIOVASCULAR PATIENT

Normal. Capillaries clearly defined; no transudation, hemorrhage, or papilledema.

RUTAMINAL* provides the extra protection of rutin and ascorbic acid...in support of the cardiotonic action of aminophylline, and the sedation of phenobarbital.

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Abnormal. Capillaries tortuous, with areas of hemorrhage and transudation. Papilledema.

RUTAMINAL...

Whenever aminophylline and phenobarbital are indicated...

*RUTAMINAL is a trademark of Schenley Laboratories, Inc., and designates exclusively its brand of tablets containing rutin, ascorbic acid, aminophylline, and phenobarbital.

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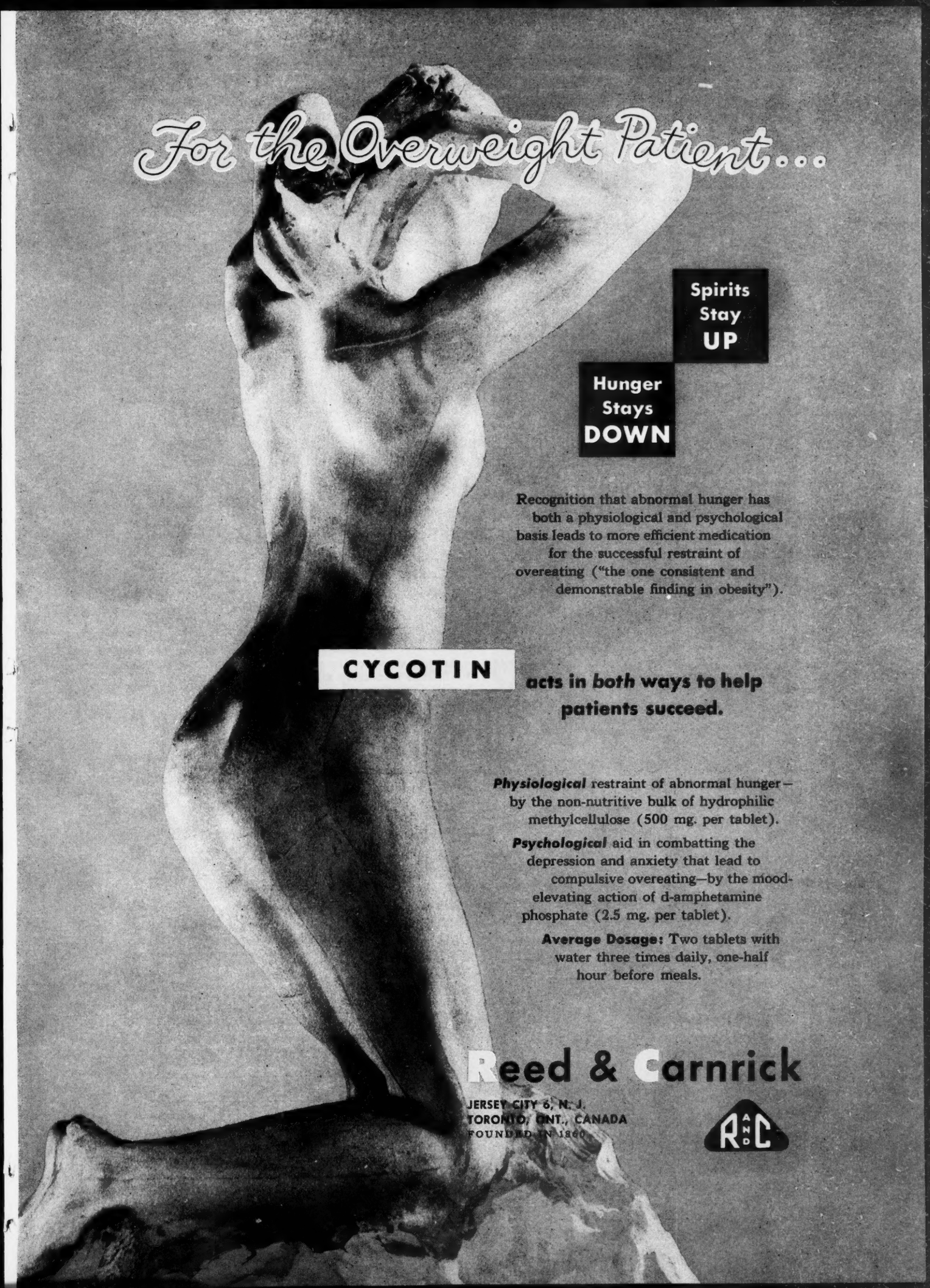
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Spirits Stay UP
Hunger Stays DOWN
Recognition that abnormal hunger has both a physiological and psychological basis leads to more efficient medication for the successful restraint of overeating ("the one consistent and demonstrable finding in obesity").
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acts in both ways to help patients succeed.
Physiological restraint of abnormal hunger—by the non-nutritive bulk of hydrophilic methylcellulose (500 mg. per tablet).
Psychological aid in combatting the depression and anxiety that lead to compulsive overeating—by the mood-elevating action of d-amphetamine phosphate (2.5 mg. per tablet).
Average Dosage: Two tablets with water three times daily, one-half hour before meals.
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FOUNDED IN 1860
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INDISPENSABLE

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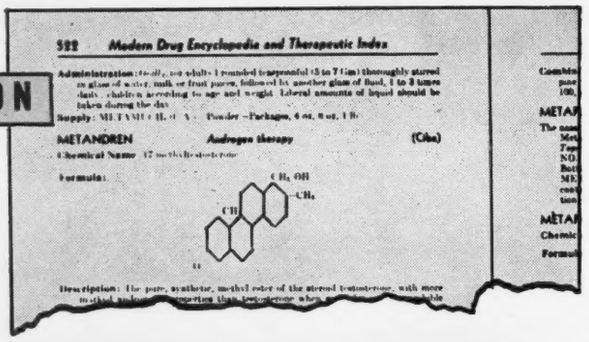
522 Modern Drug Encyclopedia and Therapeutic Index

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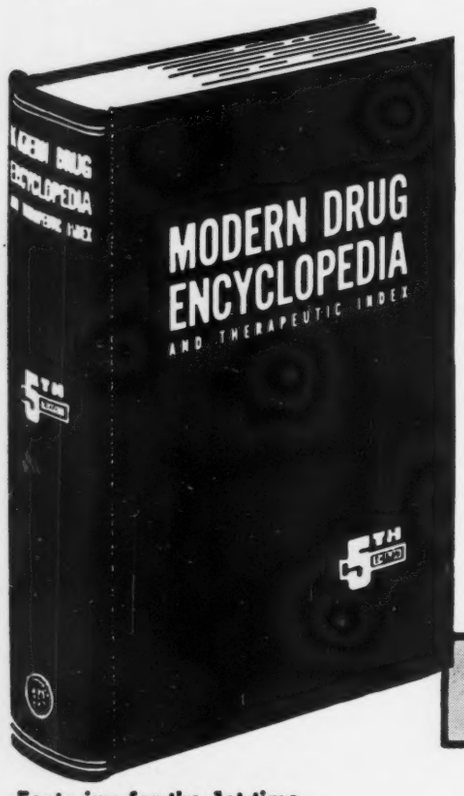
Chemical Name

Formula:

Description:



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REQUIRES NO HOSPITALIZATION

atherosclerosis

It has been found[1] that non-recurrence of myocardial infarction is associated with a dietary reduction in the blood level of the large lipoprotein molecules as determined by ultracentrifugal flotation analysis.[2] Elevated levels of these large lipoprotein molecules reflect a fundamental metabolic defect intimately related to the causation of atherosclerosis.[1]

Heparin[3] profoundly influences blood lipid transport in the human through a facilitation of the handling of fat. In this way, the use of heparin returns the level of serum lipoproteins toward the normal pattern.

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The changes produced by heparin in the level of lipoprotein molecules away from the atherosclerosis toward the normal pattern are paralleled by a genuine relief of angina pectoris. Doses of 25 to 100 mg. of heparin once or twice a week will give lasting relief independently of any anticoagulant or vasodilator action.[1]

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10 cc. vials 1000 and 5000 U.S.P. Units per cc.

is a reliable product admirably suited in these newest heparin applications in addition to its use as an anticoagulant. Neither hospitalization of patient, nor clotting time determinations are required, because of the small dosages of HED-HEPARIN needed in the management of Atherosclerosis and treatment of Angina Pectoris.

1. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B. and Nichols, A. V.: Lipoproteins in Atherosclerosis, Am. J. Med., 11:358-380 (Sept.) 1951.

2. Lyon, T. P., Jones, H. B., Graham, D. M., Gofman, J. W., Lindgren, F. T. and Yankley, A.: Further Studies on the Relationships of Sf 10-20 Lipoprotein Molecules to Atherosclerosis, Int. Med. Sect. A.M.A. Meet., Atlantic City (June 13) 1951.

3. Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J. and White, S.: Blood Lipids and Human Atherosclerosis II, The Influence of Heparin on Lipoprotein Metabolism, Circulation, IV:666 (Nov.) 1951.

*T.M.

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non-sensitizing – "We have used EURAX in approximately 400 cases. . . . There was only one instance of sensitization."

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All quotations from paper presented before the 144th Annual Meeting of the Medical Society of the State of New York, New York City, Section on Dermatology and Syphilology, May 12, 1950. Peck, S. M. and Michelfelder, T. J. New York State J. Med. *50*:1934 (Aug. 15) 1950.

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...or streptococcal pharyngitis, sinusitis, and
otitis media with many therapeutic agents...

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Pharyngitis (streptococcal)	B	A		B	B	
Sinusitis (streptococcal)	B	A		B	B	
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*KEEFER, C.S., POSTGRAD. MED. 9:101, FEB. 1951

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